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Review

Efficacy of rehabilitation programs for improving muscle strength in people with hip or knee osteoarthritis: a systematic review with meta-analysis

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SUMMARY

To analyse the effect of exercise-based rehabilitation programs for improving lower limb muscle strength in individuals with hip or knee osteoarthritis (OA). A systematic search utilizing seven databases identified randomized controlled trials (RCTs) evaluating lower limb strength outcomes of exercise-based interventions for participants with hip or knee OA. All studies were screened for eligibility and methodological quality. Quality of evidence was assessed using Grading of Recommendation, Assessment, Development and Evaluation (GRADE) approach. Data were pooled and meta-analyses performed where appropriate.

Forty RCTs were included and the majority (77%) involved resistance based exercise programs. For knee OA populations, there was high quality evidence for improved knee extension (standardized mean difference (SMD) = 0.47, 95% confidence intervals (CI) 0.29, 0.66) and flexion strength (SMD = 0.74, 95% CI 0.56, 0.92) with low-intensity resistance program when compared to a control at short term (ST) follow-up. There was moderate quality evidence for a large effect favouring high-intensity resistance programs (SMD = 0.76, 95% CI 0.47, 1.06) when compared to a control. This effect was sustained at intermediate term (IT) follow-up (SMD = 0.80, 95% CI 0.44, 1.17). Few studies reported on outcomes at long term (LT) follow-up. Only one study reported on a population with hip OA. When compared to a control group, high-intensity resistance exercise demonstrated moderate quality of evidence for large and sustained improvements for knee muscle strength in knee OA patients. Further work is needed to compare different modes of exercise at a LT follow-up for knee OA patients and to address the dearth of literature evaluating exercise interventions in people with hip OA.

Introduction

Musculoskeletal conditions like osteoarthritis (OA) are likely to pose an increasing economic burden[1] with an ageing population, increased prevalence of sedentary lifestyle and an increase in life expectancy. In consideration, the prevention and management of OA is a high priority across the world[2,3]. While the pathogenesis of the disease is not entirely understood, it has been suggested that atrophy or weakness of the periarticular muscles is implicated in the development, progression and severity of OA[4–6]. Atrophy of the muscles surrounding a joint affected by OA is common[7] and may result in impaired protective reflexes, excessive joint movement, joint instability and increased peak joint forces. Consequently, the risk of microtrauma to the articular cartilage increases and the pathobiomechanical cascade of OA evolves[5,6]. Such muscle weakness, characterised by a reduction in muscle force or motor unit activation[8], could lead to changes in gait and decreased performance in everyday functional activities[9].

Effective clinical management of hip and knee OA should therefore address the issue of muscle weakness[8]. Exercise management is considered to be an efficacious, safe and low cost treatment available to all in the community[10]. Exercise programs of sufficient intensity are described to be an effective strategy for improving muscle strength and endurance in healthy adults[11].

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However, neural sensitization and pain severity in individuals with OA[12] may impede their ability to complete higher intensity programs efficiently. Current literature evaluating rehabilitation programs for people with hip or knee OA report predominantly on outcomes related to pain and function[13] and these outcomes have also been assessed in recent reviews[14,15]. However when comparing rehabilitation programs, there is little evidence for outcomes that are related to changes in muscle strength, which can be defined as the ability of muscle to exert force[16], or indicators of muscle strength (e.g., muscle size). A single systematic review involving meta-analysis[17] that compared various rehabilitation programs in a population with knee and/or hip OA identified improvements in knee extension strength in favour of resistance exercise when compared to alternative interventions. However, the combination of the ‘alternate intervention’ group with control group data potentially dilutes the influence of the alternative intervention and inflates the effect size of the resistance programs.

Therefore the aim of this review was to evaluate the effect of current rehabilitation programs for improving muscle strength in people with hip or knee OA.

Methods

Search strategy and identification of studies

Seven databases (MEDLINE, CINAHL, SPORTDiscus, Embase, AUSPORT, COCHRANE and PEDro) were searched systematically from the earliest date available until February 2013. A keyword search was conducted using three main concepts: population, intervention and body region which were combined using the ‘AND’ Boolean operator. The keywords within the population type included OA and arthritis. Intervention type included rehabilitation, physical therapy, physiotherapy and exercise and the body regions included were the hip and knee. Synonyms within each concept were combined using the ‘OR’ operator. The search yield was imported into Endnote X6.0.1 (Thomson Reuters, USA) for evaluation.

Titles and abstracts were first screened independently by two reviewers (AZ: all papers, RG: A – K, TP: L – Z) using inclusion and exclusion criteria. The full text of remaining articles were then obtained and also screened independently by two reviewers using the same inclusion and exclusion criteria. Differences in opinion between reviewers were discussed until consensus was reached. Citation tracking using Google Scholar and reference checking of the included articles was also performed independently by two reviewers.

Study selection criteria

Population

The included studies were restricted to human studies involving patients with OA of the hip or knee with no surgical intervention. Other forms of arthritis (e.g., rheumatoid arthritis) were excluded since they may affect strength outcomes due to changes in vasculature and fibre type[18,19].

Intervention

The rehabilitation programs were required to be exercise based using voluntary contractions with a minimum duration of 6 weeks[20]. Studies involving neuromuscular stimulation or intervention aimed at improving joint flexibility (e.g., stretching) were excluded.

Comparison

All comparisons that included a control group undertaking usual care or an alternate program with or without exercise (e.g., dietary) were included. All comparison exercise programs were included if they differed from the intervention program.

Outcomes

Outcomes that were direct measures of muscle strength or indicators of muscle strength (e.g., cross sectional area (CSA) or muscle volume[21]) involving the muscles acting on the hip or knee were included if recorded before and after intervention.

Research design

Study types included were randomized controlled trials (RCTs) that reported on strength data published in peer reviewed journals. Only papers in the English language were eligible.

Data extraction

Data extraction was completed using a standardised spread sheet by one author (AZ) and verified by a second author (RG). Study data including population characteristic, descriptions of intervention programs, duration of the intervention programs, point of follow-up, and outcome measures were extracted. The relevant raw data from each included study were extracted where possible and entered directly into Review Manager Version 5.2 (RevMan) by one author (AZ) and checked by two second authors (RG, TP). Data were obtained by contacting the authors if not available.

Quality analysis

The methodological quality of included RCT studies was determined using the Physiotherapy Evidence Database (PEDro) scale[22]. The scale has a total of 11 questions and is considered to have “fair” to “good” reliability with an intraclass correlation coefficient (ICC) for the consensus rating of the total score of 0.68[23]. Previous literature[24] has validated the use of the final score after summation of the individual scale items on the PEDro scale. Quality assessments were independently evaluated by two examiners (AZ: all papers, RG: A – K, TP: L – Z) and finalized by reference to the PEDro database where possible or by consensus. No studies were excluded on the basis of quality assessment.

The GRADE approach was used to evaluate the quality of the body of evidence for outcomes that were included in a meta-analysis. This method grades the quality of the outcomes measures of interest as high, moderate, low or very low[25] using five domains: risk of bias, inconsistency, indirectness, imprecision and publication bias[25,26].

Data synthesis

In order to answer questions regarding the effectiveness of different types of exercise programs, studies were grouped based

Table I
Basis of comparisons for meta-analysis

Population	Follow-up time	Comparison groups	Muscle groups
Hip OA Knee OA	ST: 6–13 weeks IT: 14–24 weeks LT: >24 weeks	Exercise Standard rehabilitation No intervention	Knee flexors Knee extensors Hip abductors Hip adductors Hip rotators Combined hip Combined lower limb

on the population, intervention type and duration of follow-up (Table I). To reduce clinical heterogeneity, interventions were classified as aerobic, water based (hydrotherapy), low-intensity resistance, high-intensity resistance and multimodal exercise programs according to descriptions in Appendix I, where the threshold for high-intensity resistance training was based on previous criteria[11,16]. In studies where there was more than one similar exercise based intervention group, the group that demonstrated greater clinical homogeneity with other included studies was included in the meta-analysis. Intervention groups were excluded if there was insufficient data to categorise the exercise program. This process was conducted independently by all authors and finalized by consensus.

A SMD with 95% CI was used to calculate the effect size separately for each outcome (e.g., strength, CSA) using standard Cochrane guidelines where sufficient data were available (29 studies). Effect sizes could not be calculated where data was reported as medians (interquartile range) and least squares mean change. Effect size thresholds of 0.2, 0.5 and 0.8 were considered small, medium and large respectively[27]. Where study methodologies were considered adequately homogeneous and appropriate data were reported, a meta-analysis was performed using RevMan and a random effects model was used to minimize the effects of statistical heterogeneity[28]. The I^2 statistic was used for assessing heterogeneity[29] where a value of 0% was interpreted as indicating no observed heterogeneity. Values of 25%, 50% and 75% indicated low, moderate and high levels of heterogeneity and a value of 100% was considered to be a completely heterogeneous sample[29]. When no numerical data were supplied, they were estimated from graphs[30]. Where insufficient data were provided for an effect size calculation these data were requested from the original author and were described qualitatively if not provided.

Results

Yield

A total of 11,240 studies were identified through database searching and 6533 studies remained after the removal of duplicates (Fig. 1). Fifty two of the 92 full text articles obtained were excluded as outlined in Fig. 1 and the reasons for exclusion can be found in Appendix II. The final library included 40 RCTs[31–70] (Table II).

The majority of included RCTs reported on a knee OA population (35 articles). Only one article reported on a hip OA population and four articles reported on a population with a combination of hip and knee OA. Strength outcomes were most commonly reported for the knee flexors and extensors (38 articles). Other strength outcomes were reported for the hip muscles, CSA of quadriceps, combined lower limb strength and combined knee flexor and extensor strength. The studies reported on interventions that were low-intensity resistance exercise (25 studies), high-intensity resistance exercises (15 studies), multimodal exercises (seven studies), hydrotherapy (four studies) and aerobic exercise (one study). Most studies involved intervention durations that ranged from 6 to 12 weeks and only three studies reported on intervention durations that were more than 12 weeks. The follow-up periods reported varied from short term (ST: 6–13 weeks) to long term (LT: >24 weeks).

The average methodological quality score of the RCT studies was 6.1 with scores ranging from 3 to 8 out of a possible 10 (Table III). Of the included studies, 21 (52.5%) did not conceal allocation, 19 (47.5%) did not report blinding of the assessor, 19 (47.5%) did not conduct an intention to treat analysis and 14 (35%) had high drop-out rates. Items 5 and 6 relating to effective blinding of subject and therapist received no score in almost all of the included articles.

The quality of the body of evidence could be analysed for 11 outcome measures using the GRADE approach. The average quality ranged from very low to high (Appendix III, IV, V, VI) with five demonstrating moderate levels of quality, two demonstrating high levels of quality, two demonstrating low levels of quality and two showing very low quality of evidence.

Results of meta-analysis

Of the included studies, 11 had insufficient data to be included in a meta-analysis or allow the calculation of effect sizes[38,39,46–49,53,54,59,62,66]

1. **Outcomes for knee OA population**
   a. *Low-intensity resistance vs control*

   The meta-analysis for knee extension strength at ST follow-up demonstrated high quality of evidence for a small effect favouring low-intensity exercise (10 studies, 768 participants, Fig. 2), size but moderate quality of evidence for no significant effect sizes at intermediate follow-up (three studies, 261 participants, Fig. 2). Meta-analysis for knee extension strength at LT follow-up demonstrated very low quality of evidence for no significant effect (two studies, 191 participants, Fig. 2). Meta-analysis for knee flexion strength showed high quality of evidence for medium effect favouring exercise at ST follow-up (seven studies, 529 participants, Fig. 2). Two ST follow-up studies where effect sizes could not be calculated[54,62], also reported a benefit in knee muscle strength outcomes in favour of the low-intensity resistance group. A single study where effect sizes could be calculated, showed a large effect size at LT follow-up for knee flexor strength[70] (Table II).

   There were insufficient studies for a meta-analysis for hip muscle strength. A single study[33] (Table II) reported small effect sizes at ST follow-up only for hip flexion and internal rotation but not for hip abduction, adduction, extension, external rotation and knee extension. A single study reported large effect sizes for combined lower limb strength for ST follow-up[64] (Table II).

   b. *High-intensity resistance vs control*

   Meta-analysis for knee extension strength identified moderate quality of evidence for a medium effect at ST (four studies, 195 participants, Fig. 3) and low quality of evidence for a large effect at intermediate term (IT) (three studies, 129 participants, Fig. 3) in favour of the high-intensity resistance program. Meta-analysis for knee flexion strength showed moderate quality of evidence for a large effect at ST (four studies, 195 participants, Fig. 3) and low quality of evidence for a large effect at IT follow-up (two studies, 92 participants, Fig. 3). The four ST follow-up studies where effect sizes could not be calculated[46–48,59], reported a benefit in knee muscle strength (extension and flexion) outcomes in favour of the high-intensity resistance group.

   A single study reported large effect sizes for hip abduction and adduction[40] at IT follow-up (Table II). Single studies also reported a large effect size for combined lower limb strength at IT[40] and ST[64] follow-up (Table II). A single study reported no benefits for CSA for knee extensors or flexors at ST follow-up[44] (Table II).

   c. *Other forms of exercise vs control*

   Meta-analysis of knee extension strength comparing a multimodal exercise program with a control showed very low

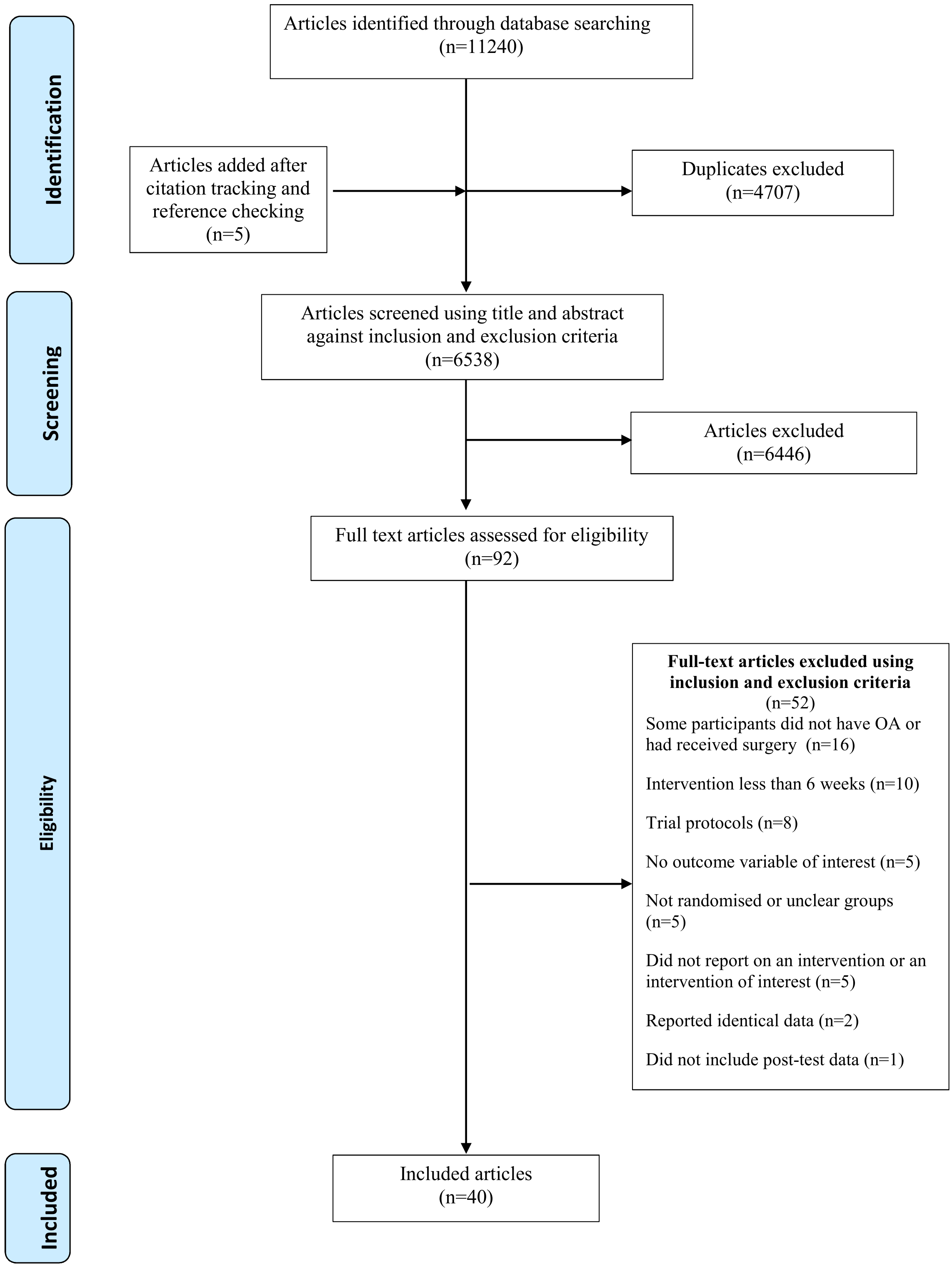


Fig. 1. Flowchart indicating process of search study selection.

quality of evidence for no significant effect at ST follow-up (two studies, 140 participants, Fig. 4). For the four single studies that reported on knee strength outcomes where effect sizes could not be calculated, two reported benefits favouring either a multimodal[49] or an aerobic group[38] while two reported no benefits favouring a multimodal[66] or a hydrotherapy group[53] when compared to a control.

d. *Comparison between two exercise groups*

Of the 10 studies that compared two exercise programs, three compared high-intensity resistance programs[44,47,58], two compared low-intensity resistance programs[35,52], and two compared a high vs low-intensity resistance program[57,64]. Single studies compared aerobic vs low-intensity resistance[38], hydrotherapy vs low-intensity resistance[53] and multimodal vs

Table II
Characteristics of included RCTs

Study	Participants	Intervention duration	Follow-up data	Comparison groups study classification (current review classification)	Outcome measure of interest	Effect size SMD (95% CI)* significant effect size
An (2008)[31]	Knee OA Total number: 28(28F, 0M) Mean age: 65	8 weeks	8 weeks (ST)	Group 1: Baduanjin group (low-intensity resistance) Group 2: No intervention (control)	Isometric strength: knee extension	(Positive − favours low-intensity resistance) Knee extension: 0.21 (−0.65, 1.07)
Baker (2001)[32]	Knee OA Total number: 46(36F, 10M) Mean age: 68	16 weeks	16 weeks (IT)	Group 1: Exercise (low-intensity resistance) Group 2: Nutrition education (control)	Isometric strength: knee flexion and extension	(Positive − favours low-intensity resistance) Knee flexion: 0.90 (0.20, 1.60)* Knee extension: 0.37 (−0.27, 1.01)
Bennell (2005a)[34]	Knee OA Total number: 140(94F, 46M) Mean age: 68	12 weeks	12 weeks (ST) and 24 weeks (IT)	Group 1: Physiotherapy (low-intensity resistance) Group 2: Placebo (control)	Isometric strength: knee extension	(Positive − favours low-intensity resistance) Knee extension: 0.06 (−0.27, 0.40)
Bennell (2010)[33]	Knee OA Total number: 89(43F, 46M) Mean age: 64	12 weeks	13 weeks (ST)	Group 1: Exercise (low-intensity resistance) Group 2: No intervention (control)	Isometric strength: hip abduction, adduction, flexion, extension, internal and external rotation and knee extension	(Positive − favours low-intensity resistance) Hip abduction: 0.33 (−0.12, 0.78) Hip adduction: 0.33 (−0.12, 0.78) Hip flexion: 0.49 (0.04, 0.95)* Hip extension: 0.30 (−0.15, 0.76) Hip internal rotation: 0.49 (0.04, 0.95)* Hip external rotation: 0.00 (−0.45, 0.45) Knee extension: 0.44 (−0.02, 0.89)
Bruce-Brand (2012)[35]	Knee OA Total number: 26(11F, 15M) Mean age: 64	6 weeks	8 (ST) and 14 weeks (IT)	Group 1: Resistance training (low-intensity resistance) Group 2: Neuromuscular electrical stimulation* Group 3: Standard care (low-intensity resistance)	Isometric strength: knee extension CSA: knee extensor	(Positive − favours low-intensity resistance) Knee extension (ST): −0.51 (−1.54, 0.52) Knee extension (IT): −0.31 (−1.33, 0.71) CSA quadriceps (ST): 0.32 (−0.56, 1.21)
Da-Hon (2007)[37]	Knee OA Total number: 81(62F, 19M) Mean age: 62	8 weeks	8 weeks (ST)	Group 1: CKCE − closed kinetic chain exercise (low-intensity resistance) Group 2: CPFE − computerised proprioception facilitation exercise* Group 3: No intervention (control)	Isokinetic strength: knee extension and flexion	(Positive − favours low-intensity resistance) Knee flexion: 0.92 (0.51, 1.32)* Knee extension: 0.51 (0.12, 0.90)*
Da-Hon (2009)[36]	Knee OA Total number: 108(75F, 33M) Mean age: 63	8 weeks	8 weeks (ST)	Group 1: Strength training of the quadriceps (low-intensity resistance) Group 2: Proprioceptive training*	Isokinetic strength: knee extension and flexion	(Positive − low-intensity resistance) Knee flexion: 0.74 (0.26, 1.22)* Knee extension: 1.04 (0.55, 1.54)*

				Group 3: No intervention (control)		
Ettinger (1997)[38]	Knee OA Total number: 439(308F, 131M) Mean age: 69	12 weeks	12 (ST), 36 (IT) and 72 (LT) weeks	Group 1: Aerobic exercise training (aerobic) Group 2: Resistance exercise training (low intensity resistance) Group 3: Health education (control)	Isometric strength: knee extension and flexion	Not estimable†
Foley (2003)[39]	Hip/knee OA or both Total number: 105(52F, 53M) Mean age: 71	6 weeks	6 weeks (ST)	Group 1: Hydrotherapy exercise (hydrotherapy) Group 2: Gym based exercise (high-intensity resistance) Group 3: No intervention (control)	Isometric strength: knee extension	Not estimable†
Foroughi (2011a)[40]	Knee OA Total number: 54(54F, 0M) Mean age: 65.5	24 weeks	24 weeks (IT)	Group 1: Progressive resistance exercise (high-intensity resistance) Group 2: Sham exercise (control)	Isometric strength: knee extension, knee flexion, combined lower limb, hip abduction and adduction	(Positive – favours high-intensity resistance) Knee flexion: 0.62 (0.02, 1.23)* Knee extension: 0.79 (0.18, 1.40)* Combined lower limb: 0.78 (0.16, 1.39)* Hip abduction: 0.81 (0.19, 1.42)* Hip adduction: 0.96 (0.34, 1.59)*
Foroughi (2011b)[41]	Knee OA Total number: 54(54F, 0M) Mean age: 64	24 weeks	24 weeks (IT)	Group 1: Progressive resistance (high-intensity resistance) Group 2: Sham exercise (control)	Isometric strength: knee extension	(Positive – favours high-intensity resistance) Knee extension: 0.58 (−0.08, 1.24)
Fransen (2001)[42]	Knee OA Total number: 126(29F, 97M) Mean age: 66	8 weeks	8 weeks (ST)	Group 1: Individual treatment dependent on the physical therapist (low-intensity resistance)‡ Group 2: Group format program 1 h twice weekly and a home based exercise program (low-intensity resistance)‡ Group 3: No intervention (control)	Isometric strength: Knee extension and flexion	(Positive – favours low-intensity resistance) Knee flexion: 0.47 (0.10, 0.84)* Knee extension: 0.48 (0.11, 0.85)*
Green (2003)[43]	Hip OA Total number: 47(35F,12M) Mean age: 67	6 weeks	12 weeks (ST)	Group 1: Home exercises + hydrotherapy (multimodal) Group 2: Home exercises only (low-intensity resistance)	Isometric strength: hip extension, abduction and internal rotation	(Positive – favours multimodal) Hip extension: 4.15 (−3.91, 12.21) Hip abduction: 16.01 (2.63, 29.39)* Hip internal rotation: 0.79 (−3.20, 4.78)
Gur (2002)[44]	Knee OA Total number: 23(Gender not reported) Mean age: 56	8 weeks	8 weeks (ST)	Group 1: Concentric exercises (high-intensity resistance)† Group 2: Concentric and eccentric exercises (high intensity resistance) Group 3: No intervention (control)	Isometric strength: knee extension and flexion CSA: knee extensor and flexor	(Positive – favours concentric exercises) Concentric vs control Knee flexion: 1.06 (−0.07, 2.18) Knee extension: 0.72 (−0.36, 1.80) CSA knee flexor: 0.18 [−0.86, 1.21]

(*continued on next page*)

Table II (*continued*)

Study	Participants	Intervention duration	Follow-up data	Comparison groups study classification (current review classification)	Outcome measure of interest	Effect size SMD (95% CI)* significant effect size
						CSA knee extensor: 0.08 [−0.95, 1.11] (Positive − favours concentric and eccentric exercises) Concentric + eccentric vs control Knee flexion: 0.77 [−0.34, 1.88] Knee extension: 0.77 [−0.34, 1.88] CSA knee flexor: 0.38 [−0.69, 1.45] CSA knee extensor: 0.29 [−0.77, 1.36] (Positive − favours concentric exercises) Concentric vs concentric + eccentric Knee flexion: 0.35 [−0.69, 1.39] Knee extension: 0.12 [−0.84, 1.07] CSA knee flexor: −0.19 [−1.15, 0.76] CSA knee extensor: −0.24 [−1.19, 0.72]
Hinman (2007)[45]	Hip or Knee OA Total number: 71(48F,23M) Mean age: 62	6 weeks	6 weeks (ST)	Group 1: Aquatic therapy (hydrotherapy) Group 2: No intervention (control)	Isometric strength: hip abduction and knee extension	(Positive − favours hydrotherapy) Knee extension: 0.46 [−0.01, 0.93] Hip abduction: 2.40 [−1.13, 5.93]
Huang (2003)[47]	Knee OA Total number: 132(93F,39M) Mean age: 62	8 weeks	8 weeks (ST)	Group1: Isokinetic exercise (high-intensity resistance) Group 2: Isotonic exercise (high-intensity resistance) Group 3: Isometric exercise (insufficient data to categorise)† Group 4: No intervention (control)	Isokinetic strength: knee extension and flexion	Not estimable†
Huang (2005a)[46]	Knee OA Total number: 120(96F, 24M) Mean age: 62	8 weeks	8 fcweeks (ST)	Group1: Isokinetic exercise (high-intensity resistance) Group 2: Isokinetic exercise + continuous ultrasound* Group 3: Isokinetic exercise + pulsed ultrasound* Group 4: No intervention (control)	Isokinetic strength: knee extension and flexion	Not estimable†
Huang (2005b)[48]	Knee OA Total number: 140(113F,27M) Mean age: 65	8 weeks	8 weeks (ST)	Group 1: Isokinetic exercise (high-intensity resistance) Group 2: Isokinetic exercise + pulse ultrasound* Group 3: Isokinetic exercise + pulse ultrasound + intra-articular hyaluronon therapy*	Isometric strength: knee extension and flexion	Not estimable†

				Group 4: No intervention (control)		
Keefe (2004)[49]	Knee OA Total number: 72(39F,33M) Mean age: 60	12 weeks	12 weeks (ST)	Group 1: Spouse-assisted pain coping skills training (SA-CST)* Group 2: SA-CST plus exercise training (SA-CST + ET)* Group 3: Exercise training alone − ET (multimodal) Group 4: Standard care (control)	Isometric strength: knee extension	Not estimable†
Krasilshchikov (2011)[50]	Knee OA Total number: 16(16F,0M) Mean age: 58	8 weeks	8 weeks (ST)	Group 1: Intervention (multimodal) Group 2: No intervention (control)	Isometric strength: knee extension	(Positive − favours multimodal) Knee extension: 1.92 (0.68, 3.16)*
Kuptniratsaikul (2002)[51]	Knee OA Total number: 392(306F, 86M) Mean age: 68	8 weeks	12 (ST), 24 (IT) and 48 (LT) weeks	Group 1: Intervention (insufficient data to categorise)† Group 2: No intervention (control)	Isometric strength: knee extension	(Positive − favours intervention) Knee extension: 0.11 (−0.09, 0.32)
Lim (2002)[52]	Knee OA Total number: 32(26F, 6M) Mean age: 60	6 weeks	6 weeks (ST)	Group 1: Open kinetic chain exercise (low intensity resistance) Group 2: Closed kinetic chain exercise (low intensity)	Isometric strength: knee extension	(Positive − favours open kinetic chain exercise) Knee extension: 0.65 (−0.06, 1.36)
Lund (2008)[53]	Knee OA Total number: 79(62F, 7M) Mean age: 68	8 weeks	8 (ST) and 20 (IT) weeks	Group 1: Aquatic exercise (hydrotherapy) Group 2: Land based exercise (low-intensity resistance) Group 3: No intervention (control)	Isometric strength: knee extension and flexion	Not estimable†
Maurer (1999)[54]	Knee OA Total number: 113(47F, 66M) Mean age: 65	8 weeks	12 weeks (ST)	Group 1: Isokinetic exercise (low-intensity resistance) Group 2: Educational intervention (control)	Isokinetic strength: knee extension	Not estimable†
McCarthy (2004)[55]	Knee OA Total number: 214(103F, 111M) Mean age: 65	8 weeks	8 (ST), 24 (IT) and 48 (LT) weeks	Group 1: Home based exercise (low-intensity resistance) Group 2: Home based exercise + class exercise program (multimodal)	Isometric strength: knee flexion	(Positive − favours low-intensity resistance) Knee flexion (ST): 0.40 (−0.14, 0.93) Knee flexion (IT): 0.17 (−0.35, 0.68) Knee flexion (LT): 0.14 (−0.47, 0.76)
McKay (2012)[56]	Knee OA Total number: 22(13F, 9M) Mean age: 62	6 weeks	6 weeks (ST)	Group 1: Intervention (low-intensity resistance) Group 2: Placebo (control)	Isometric strength: knee extension	(Positive − favours low-intensity resistance) Knee extension: 0.06 (−0.90, 1.03)
Mei-Hwa (2008)[57]	Knee OA Total number: 98(79F, 19M) Mean age: 63	8 weeks	8 weeks (ST)	Group 1: High resistance exercise (high-intensity resistance)	Isometric strength: knee extension and flexion	(Positive − favours high-intensity resistance) High-intensity resistance vs control Knee flexion: 0.74 (0.23, 1.25)*

(*continued on next page*)

Table II (*continued*)

Study	Participants	Intervention duration	Follow-up data	Comparison groups study classification (current review classification)	Outcome measure of interest	Effect size SMD (95% CI)* significant effect size
				Group 2: Low resistance exercise (low-intensity resistance) Group 3: No intervention (control)		Knee extension: 0.69 (0.19, 1.20)* (Positive − favours low-intensity resistance) Low-intensity resistance vs control Knee flexion: 0.93 (0.41, 1.45)* Knee extension: 0.59 (0.09, 1.10)* (Positive − favours high-intensity resistance) High-intensity vs low-intensity Knee flexion: −0.22 (−0.69,0.26) Knee extension: 0.06 (−0.42, 0.54)
Mei-Hwa (2009)[58]	Knee OA Total number: 106(73F, 33M) Mean age: 62	8 weeks	8 weeks (ST)	Group 1: Non weight bearing exercise (high intensity resistance) Group 2: Weight bearing exercise (high-intensity resistance)† Group 3: No intervention (control)	Isokinetic strength: knee extension and flexion	(Positive − favours non weight bearing) Non weight bearing vs control Knee flexion: 0.50 (0.02, 0.98)* Knee extension: 0.60 (0.12, 1.08)* (Positive − favours weight bearing exercise) Weight bearing vs control Knee flexion: 0.70 (0.22, 1.18)* Knee extension: 0.39 (−0.08, 0.86) (Positive − favours non weight bearing) Non weight bearing vs weight bearing exercise Knee flexion: 0.70 (0.22, 1.18)* Knee extension: 0.22 (−0.24, 0.69)
Mikesky (2006)[59]	Knee OA Total number: 221(128F, 93M) Mean age: 67	12 weeks	48 and 120 weeks (LT)	Group 1: Strength training exercises (high intensity resistance) Group 2: ROM exercises (control)	Isometric strength: knee extension and flexion	Not estimable
Peloquin (1999)[60]	Knee OA Total number: 124(87F, 37M) Mean age: 66	12 weeks	12 weeks (ST)	Group 1: Exercise group (multimodal) Group 2: 1 h education sessions (control)	Isometric strength: knee extension and flexion strength	(Positive − favours multimodal) Knee flexion: 0.40 (0.04, 0.75)* Knee extension: 0.40 (0.04, 0.75)*
Quilty (2003)[61]	Knee OA Total participants: 87(gender not reported) Mean age: 67	10 weeks	24 (IT) and 48 (LT) weeks	Group 1: Treatment group (low-intensity resistance) Group 2: No intervention (control)	Isometric strength: knee extension	(Positive − favours low-intensity) Knee extension (IT): 0.09 (−0.34, 0.52) Knee extension (LT): −0.00 (−0.44, 0.43)
Rogind (1998)[62]	Knee OA Total number: 23(21F, 2M) Mean age: 71	12 weeks	12 (ST) and 48 (LT) weeks	Group 1: Intervention (low-intensity resistance) Group 2: No intervention (control)	Isometric strength: knee extension and flexion	Not estimable†

Salli (2010)[63]	Knee OA Total number: 71(58F, 13M) Mean age: 57	8 weeks	8 (ST) and 20 (IT) weeks	Group 1: Concentric-eccentric exercise (high-intensity resistance) Group 2: Isometric exercise (insufficient data to categorise)† Group 3: No intervention (control)	Isokinetic strength: knee extension and flexion	(Positive − favours high-intensity) Concentric-eccentric vs control Knee flexion (ST): 1.53 (0.87, 2.19)* Knee flexion (IT): 1.37 (0.73, 2.01)* Knee extension (ST): 1.14 (0.52, 1.76)* Knee extension (IT): 1.01 (0.40, 1.63)* (Positive − favours isometric) Isometric vs control Knee flexion (ST): 1.21 (0.59, 1.82)* Knee flexion (IT): 1.10 (0.49, 1.71)* Knee extension (ST): 0.70 (0.12, 1.29)* Knee extension (IT): 0.66 (0.07, 1.24)* (Positive − favours group 1) Concentric-eccentric vs isometric Knee flexion (ST): 0.28 [−0.29, 0.86] Knee flexion (IT): 0.35 [−0.22, 0.93] Knee extension (ST): 0.29 [−0.29, 0.86] Knee extension (IT): 0.24 [−0.34, 0.81]
Sayers (2012)[64]	Knee OA Total number: 33(25F, 8M) Mean age: 67	12 weeks	12 weeks (ST)	Group 1: Low speed strength training (high intensity resistance) Group 2: High speed power training (low intensity resistance) Group 3: Stretching exercise (control)	Isometric strength: combined lower limb	(Positive − favours high-intensity) Low speed vs control Combined lower limb: 2.13 (1.01, 3.24)* (Positive − favours low-intensity) High speed vs control Combined lower limb: 3.79 (2.33, 5.24)* (Positive − favours high-intensity) Low speed vs high speed Combined lower limb: −0.60 (−1.46, 0.26)
Schilke (1996)[65]	Knee OA Total number: 20(17F, 3M) Mean age: 66	8 weeks	8 weeks (ST)	Group 1: Experimental group (low-intensity resistance) Group 2: No intervention (control)	Isometric strength: knee extension and flexion	(Positive − favours low-intensity) Knee flexion: 0.60 (−0.30, 1.50) Knee extension: 1.06 (0.11, 2.01)*
Sekir (2005)[66]		6 weeks	6 weeks (ST)	Group 1: Training (multimodal)	Isometric strength: knee extension and flexion	Not estimable†

(*continued on next page*)

Table II (*continued*)

Study	Participants	Intervention duration	Follow-up data	Comparison groups study classification (current review classification)	Outcome measure of interest	Effect size SMD (95% CI)* significant effect size
	Knee OA Total number: 22(16F, 6M) Mean age: 60			Group 2: No intervention (control)		
Song (2003)[67]	Knee OA Total number: 43(43F, 0M) Mean age: 64	12 weeks	12 weeks (ST)	Group 1: Tai-chi exercise (low-intensity resistance) Group 2: No intervention (control)	Isometric strength: combined knee extensor and flexor	(Positive − favours low-intensity) Combined knee: 0.31 (−0.29, 0.91)
Veenhof (2006)[68]	Hip and/or knee OA Total number: 200(154F, 46M) Mean age: 65	12 weeks	13 (ST) and 65 (LT) weeks	Group 1: Behavioural graded activity program−BGA (multimodal) Group 2: Usual care (control)	Isometric strength: knee extension, hip extension and abduction	(Positive − favours multimodal) Knee extension (ST): 0.07 (−0.22, 0.35) Knee extension (LT): 0.02 (−0.30, 0.33)
Wang, T (2007)[69]	Hip and/or knee OA Total number: 38(32F, 6M) Mean age: 66	12 weeks	12 weeks (ST)	Group 1: Aquatic programme (hydrotherapy) Group 2: No intervention (control)	Isometric strength: knee extension and flexion, hip extension, flexion, abduction and adduction	(Positive − favours hydrotherapy) Knee flexion: 0.75 (0.09, 1.41)* Knee extension: 0.73 (0.07, 1.39)* Hip flexion: 0.26 (−0.38, 0.90) Hip extension: 0.56 (−0.09, 1.21) Hip abduction: 0.59 (−0.06, 1.24) Hip adduction: 0.55 (−0.10, 1.20)
Weng, M (2009)[70]	Knee OA Total number: 132(106F, 26M) Mean age: 64	8 weeks	8 (ST) and 48 (LT) weeks	Group 1: Isokinetic exercises (low-intensity resistance) Group 2: Bilateral static stretching and isokinetic exercises* Group 3: Proprioceptive neuromuscular facilitation (PNF) stretching and isokinetic exercise* Group 4: No intervention (control)	Isometric strength: knee extension and flexion	(Positive − favours low-intensity) Knee flexion (ST): 0.79 (0.43, 1.16)* Knee flexion (LT): 1.22 (0.80, 1.63)* Knee extension (ST): 0.42 (0.07, 0.77)* Knee extension (LT): 2.11 (1.63, 2.58)*

* Group has not been used in analysis.
† Data not used for meta-analysis.
‡ Data from both groups were analysed together.

Table III
Quality assessment of RCTs using the PEDro scale

Study	Items											Total*
	1	2	3	4	5	6	7	8	9	10	11	
An *et al.*[31]	1	1	0	1	0	0	0	0	0	1	1	4
Baker *et al.*[32]	1	1	1	1	1	0	0	0	1	1	1	7
Bennell *et al.* (2005a)[34]	1	1	1	1	0	0	1	1	1	1	1	8
Bennell *et al.* (2010)[33]	1	1	1	1	0	0	1	1	1	1	1	8
Bruce-Brand *et al.*[35]	1	1	0	1	0	0	1	0	0	1	1	5
Da-Hon *et al.* (2007)[37]	1	1	0	1	0	0	0	1	0	1	0	4
Da-Hon *et al.* (2009)[36]	1	1	1	1	0	0	1	1	1	1	1	8
Ettinger *et al.*[38]	1	1	0	1	0	0	0	1	1	1	1	6
Foley *et al.*[39]	1	1	1	1	0	0	1	1	1	1	1	8
Foroughi *et al.* (2011a)[40]	1	1	0	1	1	0	0	0	0	1	1	5
Foroughi *et al.* (2011b)[41]	0	1	1	1	0	0	0	0	0	1	1	5
Fransen *et al.*[42]	1	1	1	1	0	0	0	1	1	1	1	7
Green *et al.*[43]	1	1	0	1	0	0	1	0	0	1	1	5
Gur *et al.*[44]	0	1	0	1	0	0	0	1	0	1	1	5
Hinman *et al.*[45]	1	1	1	1	0	0	1	1	1	1	1	8
Huang *et al.* (2003)[47]	1	1	1	1	0	0	0	1	0	1	1	6
Huang *et al.* (2005a)[46]	1	1	1	1	0	0	0	0	0	1	1	5
Huang *et al.* (2005b)[48]	0	1	1	1	1	0	1	1	0	1	1	7
Keefe *et al.*[49]	1	1	0	0	0	0	0	0	0	1	1	3
Krasilshchikov *et al.*[50]	1	1	0	0	0	0	1	1	1	1	1	6
Kuptniratsaikul *et al.*[51]	0	1	0	1	0	0	0	1	0	1	1	5
Lim *et al.*[52]	1	1	0	1	0	0	0	1	0	1	1	5
Lund *et al.*[53]	1	1	1	1	0	0	1	1	1	1	1	8
Maurer *et al.*[54]	1	1	0	1	0	0	1	1	0	1	1	6
McCarthy *et al.*[55]	1	1	1	1	0	0	1	0	1	1	1	7
McKay *et al.*[56]	1	1	1	1	0	0	0	0	1	1	1	6
Mei-Hwa *et al.* (2008)[57]	1	1	0	1	0	0	1	1	1	1	1	7
Mei-Hwa *et al.* (2009)[58]	1	1	0	1	0	0	1	1	1	1	1	7
Mikesky *et al.*[59]	1	1	0	1	0	0	1	0	0	1	1	5
Peloquin *et al.*[60]	1	1	0	1	0	0	1	1	0	1	1	6
Quilty *et al.*[61]	1	1	1	1	0	0	1	1	1	1	1	8
Rogind *et al.*[62]	1	1	0	1	0	0	1	1	1	1	1	7
Salli *et al.*[63]	0	1	1	0	0	0	1	1	0	1	1	6
Sayers *et al.*[64]	0	1	1	1	0	0	1	0	1	1	1	7
Schilke *et al.*[65]	0	1	0	0	0	0	0	1	0	1	1	4
Sekir *et al.*[66]	1	1	0	1	0	0	0	1	1	1	1	6
Song *et al.*[67]	1	1	1	1	0	0	0	0	0	1	1	5
Veenhof *et al.*[68]	1	1	0	1	0	0	1	1	1	1	1	7
Wang *et al.*[69]	1	1	0	1	0	0	0	1	1	1	1	6
Weng *et al.*[70]	0	1	1	1	0	0	0	0	1	1	1	6

1 – eligibility criteria specified, 2 – random allocation, 3 – concealed allocation, 4 – groups similar at baseline, 5 – subject blinding, 6 – therapist blinding, 7 – assessor blinding, 8 – less than 15% dropouts, 9 – intention-to-treat analysis, 10 – between-group statistical comparisons, 11 – point measures and variability data.
* Items 2–11.

low-intensity resistance programs[55]. Most studies reported no differences in knee strength or CSA outcomes and only one[58] (involving 71 participants) resulted in a medium effect in favour of one of the high-intensity resistance when compared to the other high-intensity resistance exercise for knee flexion strength at ST follow-up. Two studies[38,47] where effect sizes could not be calculated reported no differences when comparing two different exercise programs.

2. **Outcomes for hip OA population**
There were no comparisons of hip strength outcomes involving control groups. A single study with a ST follow-up (involving 23 participants) produced a medium effect for hip abduction strength (SMD = 0.67, 95% CI 0.08, 1.26) in favour of a multimodal group when compared to low-intensity resistance exercises, but no significant effect for hip extension or internal rotation strength[43].

3. **Outcomes for a combination of hip and knee OA**
Meta-analysis comparing hydrotherapy with a control group found moderate quality of evidence for a small effect in favour of hydrotherapy for hip abduction strength and a medium effect for knee extension strength at ST follow-up (two studies, 109 participants, Fig. 5). For the single study comparing hydrotherapy and a control group, a medium effect size was found for knee flexion strength at ST follow-up in favour of the hydrotherapy group although no significant effect for hip flexion, adduction or extension strength was identified[69] (Table II). A study comparing hydrotherapy, high-intensity resistance exercise and controls reported no differences in knee extension strength between the exercise groups but there was a significant benefit for both exercise programs when compared to the control group[39]. In a single study, a multimodal exercise program showed no benefit compared to control group for knee extension strength at ST or LT follow-up[68] (Table II).

Discussion

The studies included in this review varied widely in terms of population, comparison groups, intervention types and intervention durations. There was high quality of evidence for improved knee extension and flexion strength with low-intensity resistance programs when compared to a control at ST follow-up. There was moderate quality of evidence for large effect sizes for high-intensity resistance programs vs control at ST follow-up. Few programs reported benefits over control programs at IT or LT follow-up and there were few differences reported in outcome measures when comparing two alternate exercise programs. Only one study included muscle outcomes for a hip OA population and this study failed to identify a difference between two exercise programs for most of the hip muscle strength outcomes.

The overall methodological quality of the included studies was considered moderate[71] with an average score of 6.1; 14 studies scored 5 or less and one study only scored 3 on the PEDro scale. While it is desirable to blind therapists and patients this is almost impossible to achieve in an exercise based intervention[24,71] and therefore a quality score of 8 would be indicative of a high quality study. More than half (21 studies) did not conceal allocation which can have implications for overestimating effect sizes[72]. Failure to blind the outcome assessor could result in biased findings[73] and almost half of the included studies (19) in this review failed to score on this criterion which may be an important criterion for strength measures. Studies that follow the intention to treat principle and have decreased numbers that are lost to follow-up are more likely to provide unbiased results of treatment effects[74]. Nineteen studies in this review did not have a complete follow-up or use an intention to treat analysis and this may have also inflated effect sizes.

The overall quality of the body of evidence (GRADE ratings) ranged from low to high. Downgrading the quality of evidence was a result of inadequate sample sizes (eight outcomes), inconsistency due to large levels of heterogeneity across the included studies (two outcomes) and also weakness seen in the risk of bias domain (two outcomes). The weakness seen in the risk of bias domain reflects issues associated with the methodological quality of the included studies.

The results of the meta-analysis for knee extension strength in knee OA groups demonstrated that high-intensity resistance exercise resulted in larger strength benefits and this was also maintained at IT follow-up when compared to low-intensity exercise over controls although the quality of evidence was downgraded due to increased risk of bias and imprecision in the included studies. Exercise of sufficient intensity will create the impetus for muscle activation, initially resulting in strength changes through neural adaptation[21,75] and hypertrophy and this may explain

Study or Subgroup	Low-intensity resistance Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Knee extension strength - ST								
Bennell (2005a)	4.2	1.5	73	4.1	1.63	67	16.0%	0.06 [-0.27, 0.40]
An (2008)	39.2	11.4	11	36.2	15.8	10	4.0%	0.21 [-0.65, 1.07]
McKay (2012)	1.03	0.57	10	0.81	0.52	12	4.1%	0.39 [-0.46, 1.24]
Weng (2009)	51.1	7.6	62	47.7	8.4	66	15.1%	0.42 [0.07, 0.77]
Bennell (2010)	1.6	0.4	39	1.4	0.5	37	10.9%	0.44 [-0.02, 0.89]
Fransen (2001)	10.8	29.76	83	-2.4	22.2	43	14.0%	0.48 [0.11, 0.85]
Da-Hon (2007)	85.5	24.8	52	71.7	29	52	13.3%	0.51 [0.12, 0.90]
Mei-Hwa (2008- Low int.)	86.7	24.2	34	72.7	22.3	30	9.5%	0.59 [0.09, 1.10]
Da-Hon (2009)	89	11	36	72	20	36	9.7%	1.04 [0.55, 1.54]
Schilke (1996)	67.4	28.58	10	36.3	27.78	10	3.3%	1.06 [0.11, 2.01]
Subtotal (95% CI)			**410**			**363**	**100.0%**	**0.47 [0.29, 0.66]**
Heterogeneity: Tau² = 0.03; Chi² = 13.06, df = 9 (P = 0.16); I² = 31%								
Test for overall effect: Z = 5.08 (P < 0.00001)								
1.1.2 Knee extension strength - IT								
Bennell (2005a)	4.2	1.71	73	4.2	1.63	67	53.8%	0.00 [-0.33, 0.33]
Quilty (2003)	82.9	37.2	40	79.4	42.6	43	31.9%	0.09 [-0.34, 0.52]
Baker (2001)	19.6	14.21	19	15.5	5.6	19	14.3%	0.37 [-0.27, 1.01]
Subtotal (95% CI)			**132**			**129**	**100.0%**	**0.08 [-0.16, 0.32]**
Heterogeneity: Tau² = 0.00; Chi² = 1.02, df = 2 (P = 0.60); I² = 0%								
Test for overall effect: Z = 0.65 (P = 0.51)								
1.1.3 Knee extension strength - LT								
Quilty (2003)	73	37.4	40	73.2	44.3	43	50.1%	-0.00 [-0.44, 0.43]
Weng (2009)	54.3	3.4	56	44.3	5.8	52	49.9%	2.11 [1.63, 2.58]
Subtotal (95% CI)			**96**			**95**	**100.0%**	**1.05 [-1.02, 3.12]**
Heterogeneity: Tau² = 2.18; Chi² = 41.84, df = 1 (P < 0.00001); I² = 98%								
Test for overall effect: Z = 0.99 (P = 0.32)								
1.1.4 Knee flexion strength - ST								
Fransen (2001)	8.4	19.92	83	-0.6	17.38	43	23.7%	0.47 [0.10, 0.84]
Schilke (1996)	44.7	19.6	10	32.9	18.05	10	4.1%	0.60 [-0.30, 1.50]
Da-Hon (2009)	56	19	36	41	21	36	14.4%	0.74 [0.26, 1.22]
Weng (2009)	57.1	6.4	62	51.6	7.3	66	25.4%	0.79 [0.43, 1.16]
Da-Hon (2007)	60.9	20.4	52	40.8	23.1	52	20.1%	0.92 [0.51, 1.32]
Mei-Hwa (2008- Low int.)	61.7	20.1	34	42.5	20.8	30	12.3%	0.93 [0.41, 1.45]
Subtotal (95% CI)			**277**			**237**	**100.0%**	**0.74 [0.56, 0.92]**
Heterogeneity: Tau² = 0.00; Chi² = 3.45, df = 5 (P = 0.63); I² = 0%								
Test for overall effect: Z = 8.01 (P < 0.00001)								

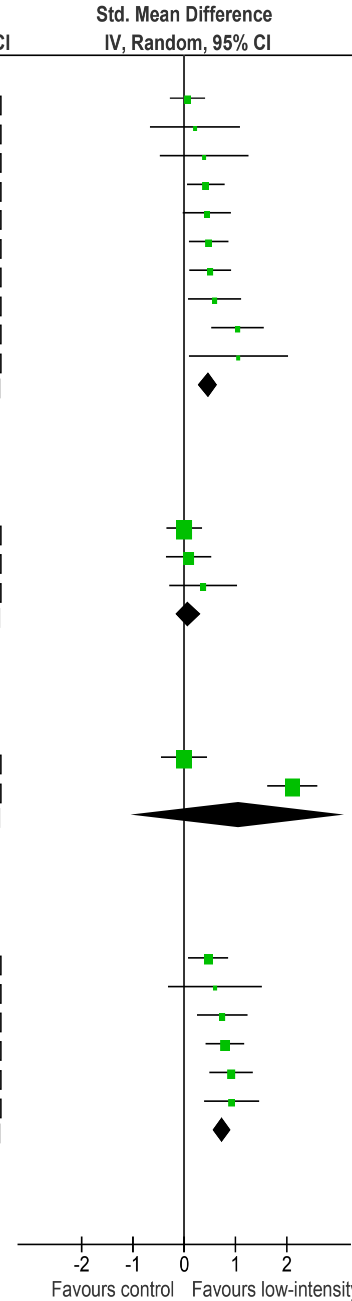


Fig. 2. Knee muscle strength outcomes for knee OA patients: low-intensity resistance vs control groups at ST and IT follow-up.

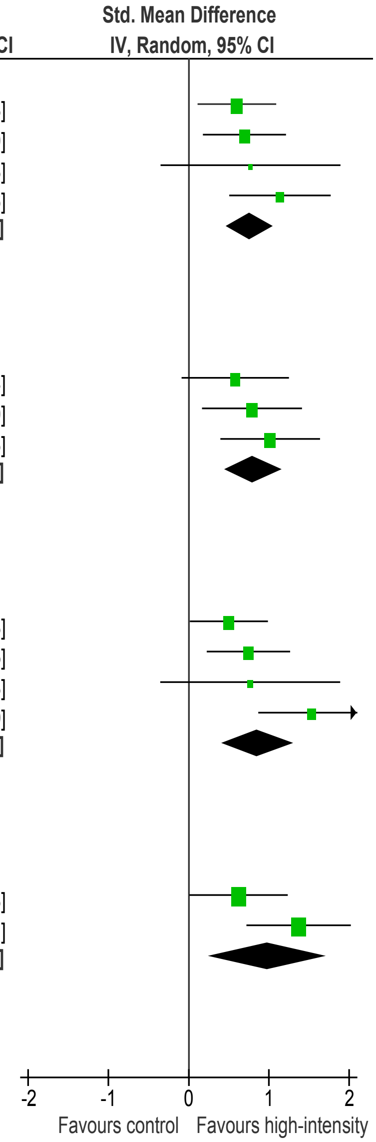
greater strength benefits associated with the high-intensity resistance programs.

There were a small number of programs that did not produce significant benefits for strength outcomes over controls and this might be the result of the low-intensity of these exercise programs or insufficient statistical power to detect an effect. Low-intensity resistance programs may not elicit adequate muscle activity to promote neuromotor adaptation and hypertrophy, which ultimately limits any gains in muscle strength[76]. In the current review, the only studies that did not produce significant strength benefits when compared to a control included exercise programs such as hydrotherapy[53] which is described to be a low-intensity exercise and multimodal exercise[66]. It is likely that the null findings in the latter study was a result of insufficient statistical power since the study by Sekir *et al.*[66] only compared 22 participants across two groups.

This review failed to identify differences in muscle strength gains when comparing two exercise programs. Similar results for functional outcomes were reported in a systematic review by Roddy *et al.*[77] when comparing aerobic exercise with strengthening exercises in people with knee OA. In contrast, the review by Latham *et al.*[17] identified improvements in knee extension strength in favour of resistance exercise when compared to alternative interventions. However as identified previously, the dilution of the “alternative intervention” group with control group data could have lead to the conflicting results in this review.

The differences identified in knee extension strength outcomes between low-intensity resistance exercise and control

Study or Subgroup	High-intensity resistance Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.1.1 Knee extension strength - ST								
Mei-Hwa (2009)	89.1	27.1	35	73.6	24	35	37.3%	0.60 [0.12, 1.08]
Mei-Hwa (2008- High int.)	88.1	21.6	34	72.7	22.3	30	33.4%	0.69 [0.19, 1.20]
Gur (2002)	8	14	8	-0.8	0.12	6	7.0%	0.77 [-0.34, 1.88]
Salli (2010)	61.89	13.76	23	47.13	11.75	24	22.3%	1.14 [0.52, 1.76]
Subtotal (95% CI)			**100**			**95**	**100.0%**	**0.76 [0.47, 1.06]**
Heterogeneity: Tau² = 0.00; Chi² = 1.91, df = 3 (P = 0.59); I² = 0%								
Test for overall effect: Z = 5.10 (P < 0.00001)								
2.1.2 Knee extension strength - IT								
Foroughi (2011b)	60.2	34.9	18	44.2	16.4	19	30.1%	0.58 [-0.08, 1.24]
Foroughi (2011a)	57.4	25.8	20	40.3	16.9	25	34.9%	0.79 [0.18, 1.40]
Salli (2010)	59.94	12.82	23	46.95	12.37	24	35.1%	1.01 [0.40, 1.63]
Subtotal (95% CI)			**61**			**68**	**100.0%**	**0.80 [0.44, 1.17]**
Heterogeneity: Tau² = 0.00; Chi² = 0.90, df = 2 (P = 0.64); I² = 0%								
Test for overall effect: Z = 4.36 (P < 0.0001)								
2.1.3 Knee flexion strength - ST								
Mei-Hwa (2009)	51.2	19.8	35	41.6	18.1	35	32.2%	0.50 [0.02, 0.98]
Mei-Hwa (2008- High int.)	57.4	18.9	34	42.5	20.8	30	30.7%	0.74 [0.23, 1.25]
Gur (2002)	24	29	8	3	20	6	12.6%	0.77 [-0.34, 1.88]
Salli (2010)	31.43	7.98	23	20.98	5.21	24	24.5%	1.53 [0.87, 2.19]
Subtotal (95% CI)			**100**			**95**	**100.0%**	**0.86 [0.40, 1.32]**
Heterogeneity: Tau² = 0.11; Chi² = 6.33, df = 3 (P = 0.10); I² = 53%								
Test for overall effect: Z = 3.69 (P = 0.0002)								
2.1.4 Knee flexion strength - IT								
Foroughi (2011a)	110.6	24.1	20	93.5	29.1	25	51.1%	0.62 [0.02, 1.23]
Salli (2010)	31.08	8.21	23	21.72	4.91	24	48.9%	1.37 [0.73, 2.01]
Subtotal (95% CI)			**43**			**49**	**100.0%**	**0.99 [0.26, 1.72]**
Heterogeneity: Tau² = 0.18; Chi² = 2.76, df = 1 (P = 0.10); I² = 64%								
Test for overall effect: Z = 2.65 (P = 0.008)								



Test for subgroup differences: Chi² = 0.38, df = 3 (P = 0.95), I² = 0%

Fig. 3. Knee muscle strength outcomes for knee OA patients: high-intensity resistance vs control groups at ST and IT follow-up.

groups at ST did not remain for most studies at longer term follow-up. The failure to maintain strength benefits at longer follow-up durations could be most likely attributed to diminishing adherence to exercise in the intervention group[78]. Adherence to an intervention program over the LT is essential to bring about benefits in outcomes[79]. There are many factors that can influence adherence to an exercise program over time, including pain and stiffness in the affected joint, the perceived

Study or Subgroup	Multimodal Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
4.1.1 Knee extension strength - ST								
Peloquin (1999)	104.88	47.04	59	88.08	37.34	65	58.0%	0.40 [0.04, 0.75]
Krasilshchikov (2011)	59.4	15.1	8	35.67	6.7	8	42.0%	1.92 [0.68, 3.16]
Subtotal (95% CI)			**67**			**73**	**100.0%**	**1.04 [-0.44, 2.51]**
Heterogeneity: Tau² = 0.95; Chi² = 5.34, df = 1 (P = 0.02); I² = 81%								
Test for overall effect: Z = 1.38 (P = 0.17)								

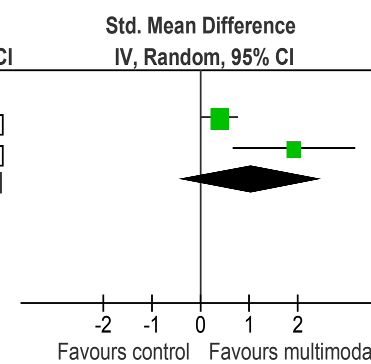


Fig. 4. Knee extension strength outcome for knee OA patients: multimodal exercise vs control groups at ST follow-up.

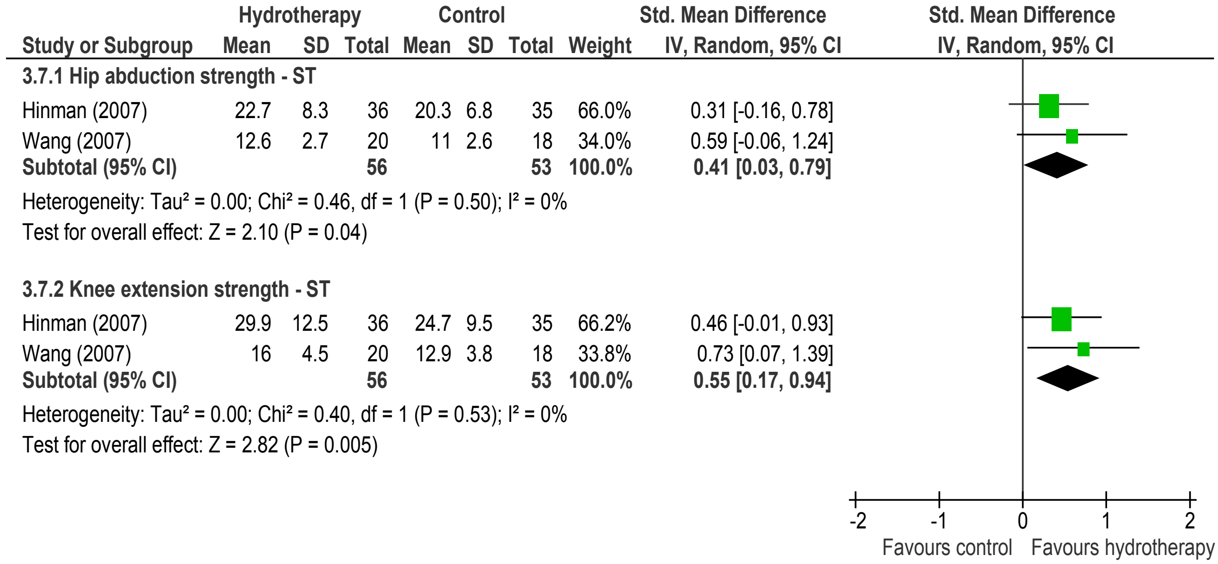


Fig. 5. Hip and knee muscle strength outcomes for hip and knee OA patients: hydrotherapy vs control groups at ST follow-up.

effectiveness of the intervention program and participant motivation to complete the intervention program over the long term[80]. The diminishing effect of exercise therapy over time as a result of poor adherence has been previously described in a systematic review of patients with hip/knee OA and it has been suggested that additional booster sessions may help to maintain LT effectiveness of an exercise program[81]. Very few of the included studies reported on LT follow-up durations.

While high-intensity resistance programs seemed to result in greater effect sizes than low-intensity resistance when compared to a control, there were no apparent differences in strength outcomes in the two studies that compared the two levels of resistance programs[57,64]. The data from these two studies could not be pooled since they reported on different outcome measures (knee strength[57] and combined limb strength[64]). Both studies had a quality score of 7, with one failing to conceal allocation[57] and the other failing to blind the outcome assessor[64]. While these failings create a potential for bias of the results, these two studies do not support high- intensity exercise over low intensity. Of note, is that strength outcome measures were taken only at ST review in both studies and thus might have missed the greater benefits achieved by high- intensity exercise over the longer term. A previous meta-analysis has shown that high-intensity resistance exercise produces greater strength benefits although the level of intensity required may vary between trained (80% 1RM) and untrained individuals (60% 1RM)[82]. Based on the findings of the current review, further high quality studies of low vs high-intensity exercise are warranted.

For hip muscle strength outcomes in a knee OA population, low-intensity resistance exercises resulted in some strength benefits at ST follow-up[33] and high-intensity resistance programs elicited greater effect sizes[40] for all hip muscle strength outcomes at longer term follow-up durations when compared to a control.

There was only one article that reported on strength outcome in a hip OA population. The hip OA population is an under-reported patient group[79,83], particularly in relation to strength outcomes[84]. Only one[43] of the six included articles in a review by McNair *et al.* reported on strength outcomes. The same study[43] was also included in the current review comparing a multimodal (home exercises with hydrotherapy) with a low-intensity resistance group (home exercises only) in a population with hip OA, and had a methodological quality score of 6 which was not different to the average score of all included studies. The study reported that a combination of hydrotherapy and home exercise resulted in some strength benefits, as long as there was compliance to the intervention program. Additional studies reporting on intervention programs in hip OA patients are required to evaluate the strength benefits for this population.

The limitations of this review were that the severity of OA was not quantified and the strength outcomes were not compared to the functional outcomes of the participants involved in the studies. Musculoskeletal change is an important determinant in levels of disability in a population with knee OA. Muscle weakness is associated with changes in gait and decreased performance in everyday functional activities[9]. While functional status is the most important outcome for patients, the relationship between programs designed to increase muscle strength and the functional outcomes requires further investigation to help refine targeted intervention programs.

The strengths of the review are that data were analysed considering different population groups (e.g., knee and hip OA), combined groups (e.g., hip and knee OA) and also different types of exercise programs, outcome measures (strength and CSA) and follow-up durations. Data were analysed by comparing either an intervention group to a control or by comparing two intervention groups and the strength outcomes were analysed separately for each intervention contrast, thus highlighting the benefits of most exercise interventions over control groups in contrast to comparisons of two exercise interventions.

Conclusion

While most exercise interventions at ST follow-up are beneficial for knee strength outcomes in knee OA patients in comparison to a control program, high-intensity resistance exercise showed low to moderate levels of quality of evidence for greater and more sustained benefits. Further investigations are warranted to explore the potential benefits of high-intensity resistance exercise over other programs. There is a dearth of studies comparing different types of exercise interventions over longer term follow-up durations. More research is needed to confirm whether exercise interventions are beneficial for hip muscles and in a hip OA population.

Author contributions

Zacharias. A designed the review, completed searches of databases, analysed and interpreted data and drafted the manuscript.
Green. R designed the review, helped in analysis and interpretation of data, helped in drafting the manuscript and revised it for important intellectual content.
Pizzari. T designed the review, helped in analysis and interpretation of data, helped in drafting the manuscript and revised it for important intellectual content.
Semciw. A helped in analysis and interpretation of data and revised the draft for important intellectual content.
Kingsley. M helped in analysis and interpretation of data and revised the draft for important intellectual content.

All authors read and approved the final draft before submission.

Conflicts of interest

None.

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Appendix I. Criteria for classification of rehabilitation programs[11,16]

Rehabilitation program	Criteria
1. Aerobic exercise	Sustained (>10 min) large body activities aimed at increasing heart rate and oxygen uptake. This category excludes water-based activities (e.g., swimming).
2. Water-based exercise	Characterised by purposeful activity that is undertaken in a water environment. Examples include hydrotherapy, swim training (any stroke)*etc*.
3. Low-intensity resistance training	Characterised by resistance training techniques including body weight exercise, weigh training, elastic devices, *etc*. Low −intensity relates to the majority of the conditioning phase being undertaken with: (primary decision) an applied resistance that is less than 70% 1RM or (secondary) repetition range ≥ 12
4. High-intensity resistance training	Characterised by resistance training techniques including body weight exercise, weight training, elastic devices, *etc*. Higher intensity relates to the majority of the conditioning phase being undertaken with: (primary decision) an applied resistance that is greater than 70% 1RM or (secondary) multiple sets of repetitions with a repetition range < 12/set.
5. Multimodal	Exercise programmes where the conditioning phase has a mixture of one or two, and three or four.

Appendix II. Table of excluded articles

Reason for exclusion	Article
Reported on an intervention period less than 6 weeks	1. Callaghan MJ, Oldham JA, Hunt J. An evaluation of exercise regimes for patients with osteoarthritis of the knee: A single-blind randomized controlled trial. Clin Rehabil. 1995;9(3):213–8. 2. Deyle G, Allison S, Matekel R. Physical Therapy Treatment Effectiveness for Osteoarthritis of the Knee: A Randomized Comparison of Supervised Clinical Exercise and Manual Therapy Procedures Versus a Home Exercise Program. Phys Ther. 2005;85:1301–17. 3. Dujin P, Jeonghee K, Hyunok L. Effectiveness of Modified Quadriceps Femoris Muscle Setting Exercise for the Elderly in Early Rehabilitation after Total Knee Arthroplasty. J Phys Ther Sci. 2012;24(1):27–30. 4. Hoeksma HL, Dekker J, Ronday HK, Heering A, Vel C, Breedveld FC *et al.* Comparison of manual therapy and exercise therapy in osteoarthritis of the hip: a randomized clinical trial. Arthritis Care Res. 2004;51(5):722–9. 5. Hurley MV. The role of muscle weakness in the pathogenesis of osteoarthritis. Rheum Dis Clin N Am. 1999;25(2):283–98. 6. Rahmann AE, Brauer SG, Nitz JC. A specific inpatient aquatic physiotherapy program improves strength after total hip or knee replacement surgery: a randomized controlled trial. Arch Phys Med Rehabil. 2009;90(5):745–55 7. Rosemffet MG, Schneeberger EE, Citera G, Sgobba ME, Laiz C, Schmulevich H *et al.* Effects of functional electrostimulation on pain, muscular strength, and functional capacity in patients with osteoarthritis of the knee. JCR. 2004;10(5):246–9. 8. Tok F, Aydemir K, Peker F, Safaz I, Taskaynatan MA, Ozgul A. The effects of electrical stimulation combined with continuous passive motion versus isometric exercise on symptoms, functional capacity, quality of life and balance in knee osteoarthritis: randomized clinical trial. Rheumatol Int. 2011;31(2):177–81. 9. Topp R, Swank AM, Quesada PM, Nyland J, Malkani A. The effect of prehabilitation exercise on strength and functioning after total knee arthroplasty. Pm R. 2009;1(8):729–35. 10. Tuzun EH, Aytar A, Eker L, Daskapan A. Effectiveness of two different physical therapy programmes in the treatment of knee osteoarthritis. Pain Clinic. 2004;16(4):379–87.
Trial protocols	1. Bennell KL, Egerton T, Wrigley TV, Hodges PW, Hunt M, Roos EM, *et al.* Comparison of neuromuscular and quadriceps strengthening exercise in the treatment of varus malaligned knees with medial knee osteoarthritis: a randomised controlled trial protocol. BMC Musculoskelet Disord. 2011;12:276. 2. Cochrane T, Davey RC, Matthes Edwards SM. Randomised controlled trial of the cost-effectiveness of water-based therapy for lower limb osteoarthritis. Health Technol Assess. 2005;9(31):iii–iv, ix–xi, 1–114. 3. Jorge R, Souza M, Chiari A, Jones A, Lombardi I, Fernandes A, *et al.* Progressive resistance exercise in women with knee osteoarthritis. Arthritis Rheum. 2010;62:2132. 4. Keogan F, Gilsenan C, Hussey J, O'Connell P. Open or closed chain quadriceps exercises in treatment of osteoarthritis of the knee; which is more effective? A blinded randomised controlled trial. Physiother Ireland. 2007;28(1):47–8 5. Lange AK, Vanwanseele B, Foroughi N, Baker MK, Shnier R, Smith RM, *et al.* Resistive Exercise for Arthritic Cartilage Health (REACH): a randomized double-blind, sham-exercise controlled trial. BMC Geriatr. 2009;9:1. 6. Lewis CB, Sterenfeld E, Danziger S, Maurer BT, Stern AG, Kinosian B, *et al.* Osteoarthritis of the knee: isokinetic quadriceps exercise versus an education intervention. Arch Phys Med Rehabil. 2000;81(4):535–6. 7. Rao A, Evans MF. Does a structured exercise program benefit elderly people with knee osteoarthritis? Can Fam Physician. 1998;44:283–4. 8. Villadsen A, Roos EM, Overgaard S, Holsgaard-Larsen A. Neuromuscular exercise improves functional performance in patients with severe hip osteoarthritis. Osteoarthritis Cartilage. 2011;19:S44.

Appendix II (*continued*)

Reason for exclusion	Article
Did not report on an outcome variable of interest	1. Gill SD, McBurney H, Schulz DL. Land-Based Versus Pool-Based Exercise for People Awaiting Joint Replacement Surgery of the Hip or Knee: Results of a Randomized Controlled Trial. Arch Phys Med Rehabil. 2009;90. 2. Kawasaki T, Kurosawa H, Ikeda H, Takazawa Y, Ishijima M, Kubota M, *et al.* Therapeutic home exercise versus intraarticular hyaluronate injection for osteoarthritis of the knee: 6-month prospective randomized open-labeled trial. J Orthop Sci. 2009;14(2):182–91. 3. Long WT, Dorr LD, Healy B, Perry J. Functional recovery of noncemented total hip arthroplasty. Clin Orthop. 1993(288):73–7. 4. Tousignant M, Moffet H, Boissy P, Corriveau H, Cabana F, Marquis F. A randomized controlled trial of home telerehabilitation for post-knee arthroplasty. J Telemed Telecare. 2011;17(4):195–8. 5. Wang TJ, Lee SC, Liang SY, Tung HH, Wu SFV, Lin YP. Comparing the efficacy of aquatic exercises and land-based exercises for patients with knee osteoarthritis. J Clin Nurs. 2011;20(17–18):2609–22.
Not randomised or groups were unclear	1. Chamberlain MA, Care G, Harfield B. Physiotherapy in osteoarthrosis of the knees: a controlled trial of hospital versus home exercises. Int Rehabil Med. 1982;4(2):101–6. 2. Eyigor S. A comparison of muscle training methods in patients with knee osteoarthritis. Clin Rheumatol. 2004;23(2):109–15. 3. Kreindler H, Lewis CB, Rush S, Schaefer K. Effects of three exercise protocols on strength of persons with osteoarthritis of the knee. Top Geriatr Rehabil. 1989;4(3):32–9. 4. Sashika H, Matsuba Y, Watanabe Y. Home program of physical therapy: effect on disabilities of patients with total hip arthroplasty. Arch Phys Med Rehabil. 1996;77(3):273–7. 5. Swanik CB, Moffit D. Strength over surgery: exercise and strength training can help knee osteoarthritis sufferers avoid surgical intervention. 2003;16(3):30–3.
All participants did not have OA or had received surgery	1. Coleman EA, Buchner DM, Cress ME, Chan BKS, De Lateur BJ. The relationship of joint symptoms with exercise performance in older adults. J Am Geriatr Soc 1996;44(1):14–21. 2. Frost H, Lamb SE, Robertson S. A randomized controlled trial of exercise to improve mobility and function after elective knee arthroplasty. Feasibility, results and methodological difficulties. Clin Rehabil. 2002;16(2):200–9. 3. Gilbey HJ, Ackland TR, Tapper J, Wang AW. Perioperative exercise improves function following total hip arthroplasty: A randomized controlled trial JMR. 2003a;7(2):111–23. 4. Krebs DE, Scarborough DM, McGibbon CA. Functional vs. strength training in disabled elderly outpatients. Am J Phys Med Rehabil. 2007;86(2):93–103. 5. LaStayo PC, Meier W, Marcus RL, Mizner R, Dibble L, Peters C. Reversing muscle and mobility deficits 1 to 4 years after TKA: a pilot study. Clin Orthop. 2009;467(6):1493–500. 6. Mei-Hwa J, Hung J, Lin JC, Wang S, Liu T, Tang P. Effects of a home program on strength, walking speed, and function after total hip replacement. Arch Phys Med Rehabil. 2004;85(12):1943–51. 7. Mikkelsen LR, Mikkelsen SS, Christensen FB. Early, Intensified Home-based Exercise after Total Hip Replacement—A Pilot Study Physiother Res Int. 2012. 8. Steinhilber B, Haupt G. Feasibility and efficacy of an 8-week progressive home-based strengthening exercise program in patients with osteoarthritis of the hip and/or total hip joint Clin Rheumatol. 2012;31:511–9. 9. Suetta C, Magnusson SP, Rosted A, Aagaard P, Jakobsen AK, Larsen LH, *et al.* Resistance training in the early postoperative phase reduces hospitalization and leads to muscle hypertrophy in elderly hip surgery patients – a controlled, randomized study. J Am Geriatr Soc. 2004;52(12):2016–22. 10. Suetta C, Andersen JL, Dalgas U, Berget J, Koskinen S, Aagaard P, *et al.* Resistance training induces qualitative changes in muscle morphology, muscle architecture, and muscle function in elderly postoperative patients. J Appl Physiol. 2008;105(1):180–6. 11. Trudelle-Jackson E, Smith SS. Effects of a late-phase exercise program after total hip arthroplasty: a randomized controlled trial. Arch Phys Med Rehabil. 2004;85(7):1056–62 12. Unlu E, Eksioglu E, Aydog E, Aydoo ST, Atay G. The effect of exercise on hip muscle strength, gait speed and cadence in patients with total hip arthroplasty: a randomized controlled study. Clin Rehabil. 2007;21(8):706–11. 13. Valtonen A, Poyhonen T, Sipila S, Heinonen A. Effects of aquatic resistance training on mobility limitation and lower-limb impairments after knee replacement. Arch Phys Med Rehabil. 2010;91(6):833–9. 14. Valtonen A, Poyhonen T, Sipila S, Heinonen A. Maintenance of Aquatic Training-Induced Benefits on Mobility and Lower-Extremity Muscles Among Persons With Unilateral Knee Replacement. Arch Phys Med Rehabil. 2011;92(12):1944–50. 15. Villalta EM, Peiris CL. Early Aquatic Physical Therapy Improves Function and Does Not Increase Risk of Wound-Related Adverse Events for Adults After Orthopedic Surgery: A Systematic Review and Meta-Analysis. Arch Phys Med Rehabil. 2013;94(1):138–48 16. Thomas KS, Muir KR, Doherty M, Jones AC, O'Reilly SC, Bassey EJ. Home based exercise programme for knee pain and knee osteoarthritis: randomised controlled trial. BMJ. 2002;325(7367):752.
Did not report on the intervention or intervention was not of interest	1. Imada K, Katoh H. Exercise Focused on Multiarticular Movement to Improve Muscle Activity During Gait and Single-leg Standing for Participants with Hip Osteoarthritis by Using Electromyogram and Three-dimensional Motion Analysis. J Phys Ther Sci. 2010;22(4):425–8. 2. Light KE, Frimel TN, Bartness WW, Villamill JM, Flynn SM. Lower extremity strength and balance after total hip arthroplasty. 2001;24(3):23–4. 3. McNair P, Simmonds M, Collier J. Effectiveness of exercise therapy in the management of osteoarthritis of the knee: a randomized control trial. Disabil Rehabil. 2007;29(20–21):1648–. 4. Russell TG, Buttrum P, Wootton R, Jull GA. Low-bandwidth telerehabilitation for patients who have undergone total knee replacement: preliminary results. J Telemed Telecare. 2003;9 Suppl 2:S44–7. 5. Russell TG, Buttrum P, Wootton R, Jull GA. Internet-Based Outpatient Telerehabilitation for Patients Following Total Knee Arthroplasty. J Bone Joint Surg Am. 2011;93-A(2):113–20.
Identical data to previous publication	1. Bennell K, Hinman R. Exercise as a treatment for osteoarthritis. Curr Opin Rheumatol. 2005b;17(5):634–40. 2. Gilbey HJ, Wang AW, Ackland TR, Morton AR, Trouchet T, Tapper J. Exercise improves early functional recovery after total hip arthroplasty. Clin Orthop. 2003b(408):193–200
No post-test data	1. Minns Lowe C, Barker KL, Holder R, Sackley CM. Comparison of postdischarge physiotherapy versus usual care following primary total knee arthroplasty for osteoarthritis: an exploratory pilot randomized clinical trial. Clin Rehabil. 2012;26(7):629–41.

Appendix III. Summary of Findings (SoF) table for low-intensity resistance vs control – Knee OA

SOF table for low-intensity resistance vs control – knee OA‡

Patient or population: Patients with knee OA
Intervention: Low-intensity resistance exercise
Comparison: Control

Outcomes	Effect size: SMD (95% CI) With low-intensity resistance exercise	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Knee extension strength – ST Follow-up: 6 – 12 weeks	SMD 0.47 (0.29–0.66)	773 (10 studies)	⊕⊕⊕⊕ **High**	Effect size: This represents a small effect
Knee extension strength – IT Follow-up: 12 – 24 weeks	SMD 0.08 (−0.16–0.32)	261 (three studies)	⊕⊕⊕⊝ **Moderate***	Effect size: This may represent no significant effect
Knee extension strength – LT Follow-up: >24 weeks	SMD 1.05 (−1.02–3.12)	191 (two studies)	⊕⊝⊝⊝ **Very low***,†	Effect size: This may represent no significant effect
Knee flexion strength – ST Follow-up: 6–12 weeks	SMD 0.74 (0.56–0.92)	514 (six studies)	⊕⊕⊕⊕ **High**	Effect size: This represents a medium effect

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
* Downgraded for imprecision (inadequate sample size).
† Downgraded for inconsistency (results were inconsistent across studies: $I^2 = 98\%$, statistical test for heterogeneity $P < 0.05$).
‡ A single study showed a large effect size SMD 1.22 (0.80–1.63) for knee flexor strength at LT follow-up. Two studies where effect sizes could not be calculated reported a benefit in knee strength outcomes favouring low-intensity exercise at ST follow-up. A single study reported small effect sizes at ST follow-up for hip flexion SMD 0.49 (0.04–0.95) and internal rotation SMD 0.49 (0.04–0.95).

Appendix IV. SoF table for high-intensity resistance vs control – knee OA

SOF table for high-intensity resistance vs control – knee OA‡

Patient or population: Patients with knee OA
Intervention: High-intensity resistance exercise
Comparison: Control

Outcomes	Effect size: SMD (95% CI) With high-intensity resistance exercise	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Knee extension strength – ST Follow-up: 6–12 weeks	SMD 0.76 (0.47–1.06)	195 (four studies)	⊕⊕⊕⊝ Moderate*	Effect size: This may represent a medium effect
Knee extension strength – IT Follow-up: 12–24 weeks	SMD 0.80 (0.44–1.17)	129 (three studies)	⊕⊕⊝⊝ Low*,†	Effect size: This may represent a large effect
Knee flexion strength – ST Follow-up: 6–12 weeks	SMD 0.86 (0.4–1.32)	195 (four studies)	⊕⊕⊕⊝ Moderate*	Effect size: This may represent a large effect
Knee flexion strength – IT Follow-up: 12–24 weeks	SMD 0.99 (0.26–1.72)	92 (two studies)	⊕⊕⊝⊝ Low*,†	Effect size: This may represent a large effect

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
A single study reported no significant benefits for CSA in knee extensors/flexors at ST follow-up.
* Downgraded for imprecision (inadequate sample size).
† Downgraded for increased risk of bias.
‡ Four studies where effect sizes could not be calculated reported a benefit in knee muscle strength favouring high-intensity resistance exercise at ST follow-up. A single study reported large effect sizes at IT follow-up for hip abduction SMD 0.81 (0.19–1.42) and adduction SMD 0.96 (0.34–1.59). Single studies reported a moderate effect at IT follow-up SMD 0.78 (0.16–1.39) and a large effect at ST follow-up SMD 3.79 (2.33–5.24) for combined lower limb strength.

Appendix V. SoF table for multimodal exercise vs control – knee OA

SOF table for multimodal exercise vs control – knee OA‡

Patient or population: Patients with knee OA
Intervention: Multimodal exercise
Comparison: Control

Outcomes	Effect size: SMD (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	With multimodal exercise			
Knee extension strength – ST Follow-up: 6–12 weeks	SMD 1.04 (−0.44–2.51).	140 (two studies)	⊕⊝⊝⊝ Very low*,†	Effect size: This may represent no significant effect

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
* Downgraded for imprecision (inadequate sample size).
† Downgraded for inconsistency (results were inconsistent across studies: $I^2 = 81\%$, statistical test for heterogeneity $P < 0.05$).
‡ Four studies where effect sizes could not be calculated, two reported a benefit favouring multimodal or an aerobic exercise while two reported no benefits favouring either a multimodal or hydrotherapy group for knee strength outcomes.

Appendix VI. SoF table for hydrotherapy vs control – hip and knee OA

Hydrotherapy vs control – hip and knee OA

Patient or population: Patients with hip and knee OA
Intervention: Hydrotherapy
Comparison: Control

Outcomes	Effect size: SMD (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	With hydrotherapy			
Hip abduction strength – ST Follow-up: 6–12 weeks	SMD 0.68 (0.51–0.85)	109 (two studies)	⊕⊕⊕⊝ Moderate*	Effect size: This may represent a medium effect
Knee extension strength – ST Follow-up: 6–12 weeks	SMD 0.55 (0.37–0.73)	109 (two studies)	⊕⊕⊕⊝ Moderate*	Effect size: This may represent a medium effect

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
* Downgraded for imprecision (inadequate sample size).

References

1. Bitton R. The economic burden of osteoarthritis. Am J Manag Care 2009;15:S230–5.
2. Australian Institute of Health and Welfare. National Health Priority Areas [21.12.13]. Available from: http://www.aihw.gov.au/national-health-priority-areas.
3. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. Bull World Health Organ 2003;81(9):646–56.
4. Hurley MV. The role of muscle weakness in the pathogenesis of osteoarthritis. Rheum Dis Clin North Am 1999;25(2):283–98.
5. Slemenda C, Brandt KD, Heilman DK, Mazzuca S, Braunstein EM, Katz BP, *et al*. Quadriceps weakness and osteoarthritis of the knee. Ann Intern Med 1997;127(2):97–104, http://dx.doi.org/10.7326/0003-4819-127-2-199707150-00001.
6. Valderrabano V, Steiger C. Treatment and prevention of osteoarthritis through exercise and sports. J Aging Res 2011;2011, http://dx.doi.org/10.4061/2011/374653.
7. Rasch A, Bystrom AH, Dalen N, Berg HE. Reduced muscle radiological density, cross-sectional area, and strength of major hip and knee muscles in 22 patients with hip osteoarthritis. Acta Orthop 2007;78(4):505–10. PubMed PMID: 17966005.
8. Loureiro A, Mills PM, Barett RS. Muscle weakness in hip osteoarthritis: a systematic review. Arthritis Care Res 2013;65(3):340–52.
9. Emrani A, Bagheri H, Hadian MR, Jabal-Ameli M, Olyaei GR, Talebian S. Isokinetic strength and functional status in knee osteoarthritis. J Phys Ther Sci 2006;18:107–14.
10. Hurley BF, Roth SM. Strength training in the elderly. Sports Med 2000;30(4):249–68, http://dx.doi.org/10.2165/00007256-200030040-00002.
11. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, *et al*. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc 2011;43(7):1334–59.
12. Arendt-Nielsena L, Niea H, Laursen MB, Laursen BS, Madeleine P, Simonsenc OH, *et al*. Sensitization in patients with painful knee osteoarthritis. Pain 2010;149(3):573–81.
13. Brosseau L, Pelland L, Wells G, Macleay L, Lamothe C, Michaud G, *et al*. Exercise of aerobic exercises for osteoarthritis (Part II): a meta-analysis. PTR 2004;9:125–45.

14. Bennell K. Physiotherapy management of hip osteoarthritis. J Physiother 2013;59:145–57.
15. Uthman OA, Van Der Windt D, Jordan JL, Dziedzic KS, Healey EL, Peat GM, *et al*. Exercise for lower limb osteoarthritis: systematic review incorporating trial sequential analysis and network meta-analysis. BMJ 2013;347.
16. ACSM's Guidelines for Exercise Testing and Prescription. 9th edn. Baltmore (MD): Lippincott Williams and Wilkins; 2014.
17. Latham N, Liu C. Strength training in older adults: the benefits for osteoarthritis. Clin Geriatr Med 2010;26(3):445–59.
18. Edstrom L, Nordemar R. Differential changes in type I and type II muscle fibres in rheumatoid arthritis: a biopsy study. Scand J Rheumatol 1974;3:155–60.
19. Sokoloff L, Wilens SL, Bunim JJ. Arteritis of striated muscle in rheumatoid arthritis. Am J Pathol 1950;27:157–73.
20. Moritani T, DeVries H. Neural factors versus hypertrophy in the time course of muscle strength gain. Amer J Physical Med 1979;59(3):115–30.
21. Frontera W, Meredith CN, O'Reilly KP, Knuttgen HG, Evans WJ. Strength conditioning in older men: skeletal muscle hypertrophy and improved function. J Appl Physiol 1988;64:1034–44.
22. Verhagen AP, de Vet HCW, de Bie RA, Kessels AGH, Boers M, Bouter LM, *et al*. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. J Clin Epidemiol 1998;51(12):1235–41.
23. Maher C, Sherrington C, Herbert R, Moseley A, Elkin M. Reliability of the PEDro scale for rating quality of randomized controlled trials. Phys Ther 2003;83:713–21.
24. de Morton NA. The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. Aust J Physiother 2009;55(2):129–33.
25. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, *et al*. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011;64(4):401–6, http://dx.doi.org/10.1016/j.jclinepi.2010.07.015.
26. Oxman AD. Grading quality of evidence and strength of recommendations GRADE working group. BMJ 2004;328:1–8.
27. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd edn. Hillsdale, New Jersey: Lawrence Erlbaum; 1988.
28. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
29. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
30. Herbert RD. How to estimate treatment effects from reports of clinical trials. I: Continuous outcomes. *Aust J Physiother* 2000;46.
31. An B, Dai K, Zhu Z, Wang Y, Hao Y, Tang T, *et al*. Baduanjin alleviates the symptoms of knee osteoarthritis. J Altern Complement Med 2008;14(2):167–74. PubMed PMID: 18315512.
32. Baker KR, Nelson ME, Felson DT, Layne JE, Sarno R, Roubenoff R. The efficacy of home based progressive strength training in older adults with knee osteoarthritis: a randomized controlled trial. J Rheumatol 2001;28(7):1655–65. PubMed PMID: 2001098074. Language: English. Entry Date: 20011026. Revision Date: 20091218. Publication Type: journal article.
33. Bennell KL, Hunt MA, Wrigley TV, Hunter DJ, McManus FJ, Hodges PW, *et al*. Hip strengthening reduces symptoms but not knee load in people with medial knee osteoarthritis and varus malalignment: a randomised controlled trial. Osteoarthritis Cartilage 2010;18(5):621–8. PubMed PMID: 20175973.
34. Bennell KL, Hinman RS, Metcalf BR, Buchbinder R, McConnell J, McColl G, *et al*. Efficacy of physiotherapy management of knee joint osteoarthritis: a randomised, double blind, placebo controlled trial. Ann Rheum Dis 2005a;64(6):906–12. PubMed PMID: 15897310; PubMed Central PMCID: PMCPMC1755542.
35. Bruce-Brand RA, Walls RJ, Ong JC, Emerson BS, O'Byrne JM, Moyna NM. Effects of home-based resistance training and neuromuscular electrical stimulation in knee osteoarthritis: a randomized controlled trial. BMC Musculoskelet Disord 2012;13:118.
36. Da-Hon L, Chien-Ho JL, Yeong-Fwu L, Mei-Hwa J. Efficacy of 2 non-weight-bearing interventions, proprioception training versus strength training, for patients with knee osteoarthritis: a randomized clinical trial. J Orthop Sports Phys Ther 2009;39(6):450–7. PubMed PMID: 19531879.
37. Da-Hon L, Yeong-Fwu L, Hei-Min C, Yueh-Chin H, Mei-Hwa J. Comparison of proprioceptive functions between computerized proprioception facilitation exercise and closed kinetic chain exercise in patients with knee osteoarthritis. Clin Rheumatol 2007;26(4):520–8, http://dx.doi.org/10.1007/s10067-006-0324-0. PubMed PMID: 2007119509.
38. Ettinger Jr WH, Burns R, Messier SP, Applegate W, Rejeski WJ, Morgan T, *et al*. A randomized trial comparing aerobic exercise and resistance exercise with a health education program in older adults with knee osteoarthritis: the Fitness Arthritis and Seniors Trial (FAST). JAMA 1997;277(1):25–31. PubMed PMID: 1997008580.
39. Foley A, Halbert J, Hewitt T, Crotty M. Does hydrotherapy improve strength and physical function in patients with osteoarthritis – a randomised controlled trial comparing a gym based and a hydrotherapy based strengthening programme. Ann Rheum Dis 2003;62(12):1162–7, http://dx.doi.org/10.1136/ard.2002.005272. PubMed PMID: 2003501710.
40. Foroughi N, Smith RM, Lange AK, Baker MK, Fiatarone Singh MA, Vanwanseele B. Lower limb muscle strengthening does not change frontal plane moments in women with knee osteoarthritis: a randomized controlled trial. Clin Biomech 2011a;26(2):167–74. PubMed PMID: 20888096.
41. Foroughi N, Smith RM, Lange AK, Fiatarone Singh MA, Vanwanseele B. Progressive resistance training and dynamic alignment in osteoarthritis: a single-blind randomised controlled trial. Clin Biomech 2011b;26(1):71–7. PubMed PMID: 20869141.
42. Fransen M, Crosbie J, Edmonds J. Physical therapy is effective for patients with osteoarthritis of the knee: a randomized controlled clinical trial. J Rheumatol 2001;28(1):156–64. PubMed PMID: 11196518.
43. Green J, McKenna F, Redfern EJ. Home exercises are as effective as outpatient hydrotherapy for osteoarthritis of the hip. Br J Rheumatol 1993;32(9):812–5.
44. Gur H, Cakin N, Akova B, Okay E, Kucukoglu S. Concentric versus combined concentric-eccentric isokinetic training: effects on functional capacity and symptoms in patients with osteoarthritis of the knee. Arch Phys Med Rehabil 2002;83(3):308–16. PubMed PMID: 2002077286. Language: English. Entry Date: 20020726. Revision Date: 20091218. Publication Type: journal article.
45. Hinman RS, Heywood SE, Day AR. Aquatic physical therapy for hip and knee osteoarthritis: results of a single-blind randomized controlled trial. Phys Ther 2007;87(1):32–43. PubMed PMID: 17142642.
46. Huang M-H, Lin Y-S, Lee C-L, Yang R-C. Use of ultrasound to increase effectiveness of isokinetic exercise for knee osteoarthritis. Arch Phys Med Rehabil 2005a;86(8):1545–51. PubMed PMID: 2009014247. Language: English. Entry Date: 20051209. Revision Date: 20091218. Publication Type: journal article.
47. Huang M-H, Lin Y-S, Yang R-C, Lee C-L. A comparison of various therapeutic exercises on the functional status of

patients with knee osteoarthritis. Semin Arthritis Rheum 2003;32(6):398–406. PubMed PMID: 2004055206. Language: English. Entry Date: 20040409. Revision Date: 20091218. Publication Type: journal article.

48. Huang M-H, Yang R-C, Lee C-L, Chen T-W, Wang M-C. Preliminary results of integrated therapy for patients with knee osteoarthritis. Arthritis Rheum 2005b;53(6):812–20. PubMed PMID: 2009706679. Language: English. Entry Date: 20071207. Revision Date: 20100730. Publication Type: journal article.
49. Keefe FJ, Blumenthal J, Baucom D, Affleck G, Waugh R, Caldwell DS, *et al*. Effects of spouse-assisted coping skills training and exercise training in patients with osteoarthritic knee pain: a randomized controlled study. Pain 2004;110(3): 539–49. PubMed PMID: 15288394.
50. Krasilshchikov O, Sungkit NB, Shihabudin TM, Shaw I, Shaw BS. Effects of an eight-week training programme on pain relief and physical condition of overweight and obese women with early stage primary knee osteoarthritis. AJPHERD 2011;17(2): 328–39. PubMed PMID: 61822291.
51. Kuptniratsaikul V, Tosayanonda O, Nilganuwong S, Thamalikitkul V. The efficacy of a muscle exercise program to improve functional performance of the knee in patients with osteoarthritis. J Med Assoc Thai 2002;85(1):33–40. PubMed PMID: 12075718.
52. Lim BW. A comparative study of open and closed kinetic chain exercise regimes in patients with knee osteoarthritis. Physiother Singapore 2002;5(2):34–40. PubMed PMID: 2003061298. Language: English. Entry Date: 20030502. Revision Date: 20091218. Publication Type: journal article.
53. Lund H, Weile U, Christensen R, Rostock B, Downey A, Bartels EM, *et al*. A randomized controlled trial of aquatic and land-based exercise in patients with knee osteoarthritis. J Rehabil Med 2008;40(2):137–44. PubMed PMID: 2009874457. Language: English. Entry Date: 20080509. Revision Date: 20101231. Publication Type: journal article.
54. Maurer BT, Stern AG, Kinossian B, Cook KD, Schumacher Jr HR. Osteoarthritis of the knee: isokinetic quadriceps exercise versus and educational intervention. Arch Phys Med Rehabil 1999;80(10):1293–9, http://dx.doi.org/10.1016/S0003-9993%2899%2990032-1. PubMed PMID: 1999352680.
55. McCarthy CJ, Mills PM, Pullen R, Richardson G, Hawkins N, Roberts CR, *et al*. Supplementation of a home-based exercise program with a class-based programme for people with osteoarthritis of the knee: a randomised controlled trial and health economic analysis. Health Technol Assess 2004;8(46).
56. McKay C, Prapavessis H, Doherty T. The effect of a prehabilitation exercise program on quadriceps strength for patients undergoing total knee arthroplasty: a randomized controlled pilot study. Phys Med Rehabil 2012;4(9):647–56, http://dx.doi.org/10.1016/j.pmrj.2012.04.012. PubMed PMID: 22698852.
57. Mei-Hwa J, Jiu-Jeng L, Jiann-Jong L, Yeong-Fwu L, Da-Hon L. Investigation of clinical effects of high- and low-resistance training for patients with knee osteoarthritis: a randomized controlled trial. Phys Ther 2008;88(4):427–36. PubMed PMID: 31976836.
58. Mei-Hwa J, Chien-Ho L, Yeong-Fwu L, Jiu-Jenq L, Da-Hon L. Effects of weight-bearing versus nonweight-bearing exercise on function, walking speed, and position sense in participants with knee osteoarthritis: a randomized controlled trial. Arch Phys Med Rehabil 2009;90(6):897–904. PubMed PMID: 19480863.
59. Mikesky AE, Mazzuca SA, Brandt KD, Perkins SM, Damush T, Lane KA. Effects of strength training on the incidence and progression of knee osteoarthritis. Arthritis Rheum 2006;55(5):690–9. PubMed PMID: 17013851.
60. Peloquin L, Bravo G, Gauthier P, Lacombe G, Billiard J-S. Effects of a cross-training exercise program in persons with osteoarthritis of the knee. A randomized controlled trial. J Clin Epidemiol 1999;5(3):126–36. PubMed PMID: 1999200894.
61. Quilty B, Tucker M, Campbell R, Dieppe P. Physiotherapy, including quadriceps exercises and patellar taping, for knee osteoarthritis with predominant patello-femoral joint involvement: randomized controlled trial. J Rheumatol 2003;30(6):1311–7. PubMed PMID: 12784408.
62. Rogind H, Bibow-Nielsen B, Jensen B, Moller HC, Frimodt-Miller H, Bliddal H. The effects of a physical training program on patients with osteoarthritis of the knees. Arch Phys Med Rehabil 1998;79(11):1421–7. PubMed PMID: 1999031763. Language: English. Entry Date: 19990501. Revision Date: 20091218. Publication Type: journal article.
63. Salli A, Sahin N, Baskent A, Ugurlu H. The effect of two exercise programs on various functional outcome measures in patients with osteoarthritis of the knee: a randomized controlled clinical trial. Isokinet Exerc Sci 2010;18(4):201–9. PubMed PMID: 2010857265. Language: English. Entry Date: 20110121. Revision Date: 20111209. Publication Type: journal article.
64. Sayers SP, Gibson K, Cook CR. Effect of high-speed power training on muscle performance, function, and pain in older adults with knee osteoarthritis: a pilot investigation. Arthritis Care Res 2012;64(1):46–53, http://dx.doi.org/10.1002/acr.20675. PubMed PMID: 2011427512. Language: English. Entry Date: 20120309. Revision Date: 20120309. Publication Type: journal article.
65. Schilke JM, Johnson GO, Housh TJ, O'Dell JR. Effects of muscle-strength training on the functional status of patients with osteoarthritis of the knee joint. Nurs Res 1996;45(2): 68–72.
66. Sekir U, Gur H. A multi-station proprioceptive exercise program in patients with bilateral knee osteoarthrosis: functional capacity, pain and sensorimotor function. J Sports Sci Med 2005;4:590–603.
67. Song R, Lee E-O, Lam P, Bae S-C. Effects of tai chi exercise on pain, balance, muscle strength, and perceived difficulties in physical functioning in older women with osteoarthritis: a randomized clinical trial. J Rheumatol 2003;30(9):2039–44. PubMed PMID: 12966613.
68. Veenhof C, Koke AJA, Dekker J, Oostendorp RA, Bijlsma JWJ, van Tulder MW, *et al*. Effectiveness of behavioral graded activity in patients with osteoarthritis of the hip and/or knee: a randomized clinical trial. Arthritis Rheum 2006;55(6):925–34. PubMed PMID: 17139639.
69. Wang T-J, Belza B, Thompson FE, Whitney JD, Bennett K. Effects of aquatic exercise on flexibility, strength and aerobic fitness in adults with osteoarthritis of the hip or knee. J Adv Nurs 2007;57(2):141–52. PubMed PMID: 17214750.
70. Weng M-C, Lee C-L, Chen C-H, Hsu J-J, Lee W-D, Huang M-H, *et al*. Effects of different stretching techniques on the outcomes of isokinetic exercise in patients with knee osteoarthritis. Kaohsiung J Med Sci 2009;25(6):306–15. PubMed PMID: 19560995.
71. Moseley MA, Herbert RD, Sherrington C, Maher CG. Evidence for physiotherpay practice: a survey of the Physiotherapy Evidence Database (PEDro). Aust J Physiother 2002;48:43–9.
72. Juni P, Altman DG, Egger M. Assessing the quality of controlled clinical trials. BMJ 2001;323:42–6.
73. Poolman RW, Struijs PAA, Krips R, Sierevelt IN, Marti RK, Farrokhyar F, *et al*. Reporting of outcomes in orthopaedic randomized trials: does blinding of outcome assessors matter? J Bone Joint Surg 2007;89-A(3):550–8, http://dx.doi.org/10.2106/JBJS.F.00683.

74. Montori VM, Guyatt GH. Intention-to-treat principle. Can Med Assoc J 2001;165(10):1339–41.
75. Goldspink DE. The influence of activity on muscle size and protein turnover. J Physiol 1977;264:283–96.
76. Buchner DM. Understanding variability in studies of strength training in older adults: a meta-analytic perspective. Top Geriatr Rehabil 1993;8(3):1–21.
77. Roddy E, Zhang W, Doherty M. Aerobic walking or strengthening exercise for osteoarthritis of the knee? A systematic review. Ann Rheum Dis 2005;64(4):544–8. PubMed PMID: 15769914; PubMed Central PMCID: PMCPMC1755453.
78. van Baar ME, Dekker J, Oostendorp RAB, Bijl D, Voorn TB, Bijlsma JWJ. Effectiveness of exercise therapy in patients with osteoarthritis of the hip or knee: a systematic review of randomized clinical trials. Arthritis Rheum 2001;42(7):1361–9. PubMed PMID: 1999078874. Language: English. Entry Date: 19991201. Publication Type: journal article.
79. Fransen M, McConnell S, Bell M. Exercise for osteoarthritis of the hip or knee. Cochrane Database Syst Rev 2003;3.
80. Campbell R, Evans M, Tucker M, Quilty B, Dieppe P, Donovan J. Why don't patients do their exercises? Understanding non-compliance with physiotherapy in patients with osteoarthritis of the knee. J Epidemiol Community Health 2001;55(2):132–8.
81. Pisters MF, Veenhof C, van Meeteren NL, Ostelo RW, de Bakker DH, Schellevis FG, *et al*. Long-term effectiveness of exercise therapy in patients with osteoarthritis of the hip or knee: a systematic review. Arthritis Rheum 2007;57:1245–53.
82. Rhea MR, Alvar BA, Burkett LN, Ball SD. A meta-analysis to determine the dose response for strength development. Med Sci Sports Exerc 2003;35(3):456–64.
83. Bartels EM, Lund H, Hagen KB, Dagfinrud H, Christensen R, Danneskiold-Samsoe B. Aquatic exercise for the treatment of knee and hip osteoarthritis. Cochrane Database Syst Rev 2007;4. PubMed PMID: 2009825135. Language: English. Entry Date: 20080314. Revision Date: 20110715. Publication Type: journal article.
84. McNair PJ, Simmonds MA, Boocock MG, Larmer PJ. Exercise therapy for the management of osteoarthritis of the hip joint: a systematic review. Arthritis Res Ther 2009;11(3):R98. PubMed PMID: 19555502; PubMed Central PMCID: PMCPMC2714154.